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LEPTOSPIROSIS IN ENGLAND AND WALES*

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Human leptospirosis is not a disease which presents the dramatic situations demanding instant action provided by sweeping epidemics of, say, plague and cholera. On the contrary, it is an insidious infection which has crept into our midst and has established itself almost unnoticed. It is recognized as a hazard attached to certain occupations, such as coal-mining and work in sewers, but the affection claims a toll of victims from other sections of the population—and does so almost unperceived.

It is perhaps natural for us to think of leptospirosis mainly as a group of diseases affecting man and some of his domestic animals. In fact, however, leptospires are primarily parasites of rodents, chiefly rats and mice, though some have become adapted to pigs, cattle, or dogs. In many cases the micro-organisms are so well adapted to their normal hosts that they establish large colonies in the tubules of the kidneys, and exist there as commensals without apparently producing any deleterious effect on the animal host.

Intermittently some of the leptospires pass down the kidney tubules and are shed with the urine. If they reach water which provides suitable conditions the organisms can survive for days or even weeks. They enter new hosts either through broken skin or mucous surfaces, and so the cycle continues.

If the new host happens to be man or a susceptible domestic animal, pathological effects are produced and disease results. Although this is an accidental occurrence, it is one with important consequences from the human standpoint, and most investigators have directed their attention to the effects which follow infection of these casual hosts. There is evidence, however, which is put forward later, that fuller studies of the metabolism of the leptospire, and of the ecology of its natural hosts, might yield information of great value in the prevention of leptospirosis.

The first pathogenic leptospire to be isolated from man was the causal organism of Weil's disease. The discovery was reported in Japanese by Inada and Ido during February, 1915, and the micro-organism was named by them *Spirochaeta icterohaemorrhagiae*. A full record of these investigations was made in English by Inada, Ido, Hoki, Kaneko, and Ito (1916). Noguchi (1917) considered the morphology of this organism to be sufficiently characteristic to warrant the creation of a new genus, which he named *Leptospira*.

[*At this period the lecturer dealt with the classification and description of different species of Leptospira.*]

*The Milroy Lectures (abridged), delivered to the Royal College of Physicians on February 13 and 15, 1951.

In Table I are set forth the names and certain other characteristics of the species to which frequent reference will be made. The table also serves to illustrate how widely some species are distributed as compared with others.

TABLE I.—*Species of Leptospires*

Species	Carrier	Disease	Distribution
L. icterohaemorrhagiae	*Rattus norvegicus* (sewer rat). Other rats, and mice	Weil's disease; infectious jaundice	Almost world-wide
L. canicola ..	Dog	Canicola fever	Almost world-wide
L. grippotyphosa	*Microtus arvalus* (field vole)	Harvest, mud, field fever	Europe, Asia
L. pomona ..	Pig	Swineherd's disease	Europe, Asia, America, Australia
L. sejroe ..	*Mus spicilegus* (gleaner mouse)	Sejroe fever	Denmark, Central Europe
L. saxkoebing	*Apodemus flavicollis* (harvest mouse)	—	Denmark
L. bataviae	*R. norvegicus*	Indonesian Weil's disease	Indonesia
	A. sylvaticus (long-tailed field mouse)	Ricefield fever	Central Europe

There are equally marked differences in the number of species found in any particular locality. Collier (1948) states that 18 antigenically distinct species have been isolated in the Netherlands Indies. In Australia, five species are known to cause disease in man (Johnson, 1950). A large variety of serological types were isolated in the Belgian Congo by van Riel (1946). He did not regard their antigenic constitution as distinctive enough to warrant the establishment of separate species, and their relationships remain to be fully worked out and compared with known species.

In Central Europe, human infections have been reported with nine separate species. In addition to those shown in Table I there are *L. mitis*, a species which was first discovered in Australia by Johnson (1942), and *L. ballum* (Borg Petersen, 1944). Only one human infection with *L. ballum* has been reported (Borst, Ruys, and Wolff, 1948).

All cases of leptospirosis so far recognized in this country have been due to *L. icterohaemorrhagiae* and *L. canicola*. We have therefore tried to obtain information about the presence of other species by seeking evidence of human infections. Meningitis is one of the outstanding symptoms of the disease which these species produce in man, so we have tested serum from cases of meningitis for the presence of leptospiral antibodies. Through the kindness of Dr. F. O. MacCallum, of the Virus Reference Laboratory, London, we have been

able to examine serum from 642 cases of aseptic meningitis. The sera had previously been tested to exclude viral infections.

L. bataviae, L. grippotyphosa, L. pomona, and L. sejroe were chosen as a representative series, and the agglutination reactions of the sera were tested against these species, as well as against the two indigenous ones. In not a single instance was there the slightest indication of infection with any of the "foreign" species, although 17 cases of the pure meningeal form of Weil's disease and 8 of canicola fever were brought to light.

These investigations are being continued, and rodent surveys will be made if opportunity affords. From the evidence at present available, however, it appears that if other species of leptospires do exist in England they seldom if ever produce recognizable disease in man.

Leptospirosis in Domestic Animals

A number of species of leptospires can attack domestic animals, and at least two—*L. canicola* and *L. pomona*—seem to have no rodent hosts, depending for their propagation on dogs and pigs respectively. In this country, as far back as 1925, Okell, Dalling, and Pugh found that *L. icterohaemorrhagiae* was the cause of "yellows" in dogs—a severe and often fatal illness characterized by jaundice and prostration. As this leptospire is carried by rats, the disease is found more often in kennels—among foxhounds, for example—than in dogs kept as domestic pets.

Sporadic cases of jaundice, and also small but severe epidemics, in cattle and in pigs have also been traced to infection with *L. icterohaemorrhagiae* by Field (1949) and Field and Sellers (1950 ; 1951).

However, the most widespread disease of domestic animals is canicola fever in dogs. *L. canicola* is nearly as ubiquitous as *L. icterohaemorrhagiae*, and surveys in Scotland by Stuart (1946) and in England by Broom and MacIntyre (1948) have shown that from 25 to 40% of dogs become infected at some period during their lifetime. In typical cases the disease presents the symptoms of acute interstitial nephritis, and if the dog recovers it continues to excrete leptospires for some months at least, and probably a great deal longer. For as long as dogs continue to excrete leptospires they remain a potential source of danger to other dogs, and also to humans—because *L. canicola* is also pathogenic for man. In addition to these acute cases, many dogs become infected, and act as carriers, without presenting any signs of illness at all.

Leptospirosis in Man

The best-known and the most widely distributed form of the human disease is of course leptospirosis icterohaemorrhagica. It was also the first variety to be recognized as a clinical entity, though when Goldschmidt (1887) applied the term "Weil's disease" to the syndrome portrayed by Weil (1886) the aetiology was quite unknown. As noted above, *L. icterohaemorrhagiae* was not isolated until 30 years later, by Inada and his colleagues in Japan in 1915.

Weil's Disease

Since the middle of 1947 we have acted as the Leptospira Reference Laboratory for the Public Health Laboratory Service covering England and Wales, and in consequence we have an almost complete record of all the cases of leptospirosis which have been recognized in these countries during the past few years.

Within the period under review 465 cases of Weil's disease have been diagnosed in England, Wales, and Northern Ireland. In addition, there were 70 human cases of canicola fever in the two former countries. No case of the latter form of leptospirosis has yet been reported from any part of Ireland, although a survey we made of dogs in Dublin showed the canine infection rate there to be as high as it is in England.

The present series of cases of Weil's disease shows certain marked differences from an earlier one (Broom and Alston, 1948) which covered the years from 1940 to 1946. The death rate, which was 22% among the earlier cases, has now dropped to 15%, and the proportion of patients with jaundice has fallen from 90% to 74%. These two findings are in all probability closely related, for it is generally agreed that the death rate is negligible in non-icteric cases. We know of only one death without jaundice, and, so far as we are aware, no others have been reported in the literature. The importance of distinguishing between the icteric and non-icteric forms of Weil's disease will be apparent when the value of penicillin in treatment is under consideration later.

TABLE II.—*Weil's Disease: Age Incidence, Recoveries, and Deaths*

	Age in Years					Total	Age Unknown
	Up to 15	16–30	31–45	46–60	Over 60		
Recoveries ..	35	97	78	67	17	294	7
Deaths	0	3	24	23	7	57	1
Outcome unknown	1	2	4	3	0	10	49
Total cases ..	36	102	106	93	24	361	57
Case mortality ..	0	3	24	25	29	16	—

Age Incidence and Death Rate.—The age incidence and the death rates at different ages are shown in Table II. The low mortality figure for patients under 30 is in marked contrast to the heavy death roll in the later age groups. The data have been analysed in a number of ways, but no indication has been found that factors other than age had any special significance.

Sex Incidence.—In this series there were 26 females and 439 males. The high preponderance of men (95%) is the usual finding, except among fish-cleaners, an occupation in which most of the workers are women. When the chance of infection is the same there is no difference in the incidence between the two sexes.

Seasonal Incidence of Weil's Disease

Fig. 1 shows diagrammatically the monthly incidence of Weil's disease. The monthly totals in each case have been expressed as a percentage of the corresponding totals for the whole period, and the ordinate scale in the upper diagram has been reduced to one-half of that used for the other two. These expedients were adopted for ease of visual comparison, and the appropriate totals are inserted in each chart. In carrying out this analysis, the cases were allocated to the various months according to the date of the onset of symptoms. The actual infection must have occurred from one to two weeks earlier, but the length of the incubation period is seldom known with any degree of accuracy. On the other hand, the date of onset is easily determined, and has been used for that reason.

The incidence of bathing infections is represented in the upper histogram and, as is to be expected, a strongly

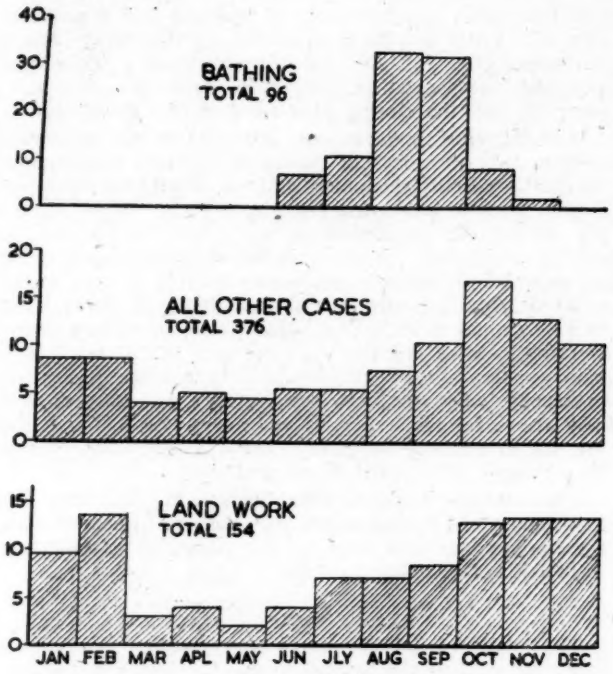

FIG. 1.—Percentage monthly incidence of Weil's disease.

marked seasonal influence is apparent. The first cases appear in June, and two-thirds of the total occurred during August and September.

All cases, except those due to bathing, are included in the middle histogram. The seasonal variation is much less obvious in this instance, but there is a decided tendency for the numbers to increase in the late summer and autumn, and to fall to a minimum during spring and early summer. The reason for this rhythm is unknown, but it may be one of the matters on which light would be cast by a study of the ecology of the rodent carriers, and of the metabolism of the leptospires.

The incidence among agricultural workers has been charted separately, for a reason explained later, although these cases are included in the centre histogram also. It will be noted that the autumnal rise in incidence is maintained throughout the winter, and that the infection rate remains low during spring and early summer. It may perhaps be conjectured that the rat population around farmyards and buildings rises when the harvest has been brought in from the fields. Certainly large numbers of rats are disturbed and killed when threshing operations are in progress, and the chances of contamination with infective urine must be very high at these times. We heard recently, for instance, of a farm on which no fewer than 600 rats were destroyed during the threshing of a single stack of grain.

Occupational Incidence of Weil's Disease

In Table III is set out the manner in which infection was contracted, so far as it was related to occupation or avocation. The most striking feature is the very high place occupied by agricultural workers, who constitute nearly one-third of the total number of cases. On the other hand, sewer-workers and coal-miners, whose work is recognized as carrying a special risk of infection, contribute together rather less than one-half as many cases as resulted from bathing.

It should be noted that persons handling food provide as many cases as do coal-miners. This category includes butchers, but for the most part the patients were employed in establishments where food was prepared for human consumption. It therefore seems that the level of hygiene in a number of such places still leaves much to be desired.

The "miscellaneous" group contains a few cases in which no obvious source of infection could be traced, but as a rule the possibility of contact with rat urine was quite clear. For example, some of the patients were rat-catchers, or men who had handled or had been bitten by rats; some were artisans whose work took them into rat-infested buildings; some lived in rat-ridden houses; and some had run the risk of infection in various ways, perhaps on a single occasion only.

TABLE III.—*Occupational Incidence of Weil's Disease, 1947–50 (418 Cases)*

	%
Farm-workers	31
Bathing and accidental immersion	19
Sewer-workers	5
Coal-miners	4
Handlers of food	4
Fish-workers	3·5
Working in water	2·5
Miscellaneous	31

Agriculture

The association between work on the land and certain forms of leptospirosis is of course well known. One may cite, for instance, canefield fever in sugar-cane workers in Queensland, Australia (Johnson, 1950); sejroe fever in harvesters in Denmark (Borg Petersen, 1949); the many epidemics of mud-fever (Kathe, 1950); and *L. bataviae* infections in the rice fields of Italy (Mino, 1938). A high incidence of true Weil's disease in agricultural workers in Japan was noted by Tohyama (1924), but the frequency of its occurrence in land-workers in other countries is not perhaps always appreciated—indeed, it is not even mentioned by Walch-Sorgdrager (1939) in her very extensive monograph on leptospirosis.

However, over 30% of the patients in this present series were engaged in agricultural work. Over the past 15 years there has been an increase both in the number of cases in farm-workers and in the fraction which they constitute of the total of all cases. It is difficult to decide whether this

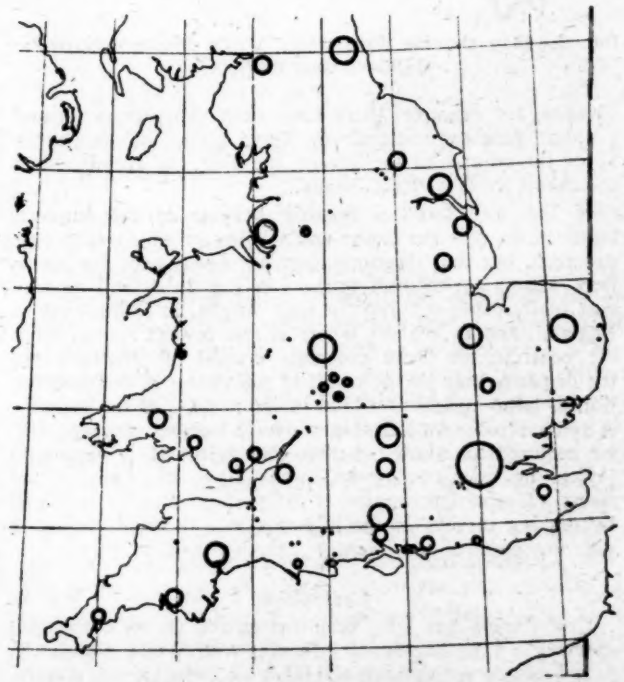

FIG. 2.—Map showing distribution of Weil's disease, 1947–50.

is the result of improved diagnostic facilities or whether it represents a true rise in incidence in agricultural districts.

In this connexion it is interesting to note that Adam (1950), who analysed the distribution of Weil's disease in North Germany, found the disease to be limited, in the main, to the lower reaches and the estuaries of the great rivers and their tributaries. In purely rural areas, away from the rivers, the incidence was low. Fig. 2 shows the distribution of cases of Weil's disease in England and Wales during the last few years. The size of the circles indicates approximately the relative numbers reported from the different areas.

In this country, of course, there is no wide hinterland, far removed from river estuaries, but the diagram suggests that there is a tendency for cases to cluster about the mouths of rivers and along their courses. In the valley of the

FIG. 3.—Map showing areas where Weil's disease occurred in farm-workers, 1947–50.

Thames, for example, there have been many cases around London, Reading, and Oxford. Other groups of cases occur along the courses of the Severn, the Test, the Humber, and the many rivers of East Anglia.

In Fig. 2 it was not feasible, because of the numbers involved, to plot the towns and villages in which each case occurred, but that discrimination has been made for infections among agricultural workers in Fig. 3. It will be seen that many cases occurred in East Anglia, in South-western England, and in Wales. There is less inward spread from the coast in the more northerly centres of infection, but the disparity may be the result of differences in the distribution of good agricultural land in divers parts of the country. A series of observations, taken over a number of years, will be required to show whether the infection is gradually infiltrating from the coastal areas along the lines of the rivers. Useful information could perhaps also be obtained by making surveys of the infection rate in rats, trapped in different parts of the country, over a period of years.

Coal-mining

Coal-mining has long been recognized as an occupation carrying a high hazard of infection with Weil's disease.

In contrast to the high incidence recorded in this country in the past, the total number of cases reported during the past four years for the whole of England and Wales was only 15. From our inquiries it appears that three factors are responsible for the reduced incidence. These are increased mechanization, improved methods of water-pumping, and the closing of a number of "drift" mines.

Mechanization involves the introduction of conveyer-belts to take the place of ponies or horses. This change drastically curtails the potential food supply of rats, and thereby leads to a decrease in their numbers. Better pumping reduces the proportion of wet mines, which provide suitable conditions for the survival of leptospires shed in rat urine. Drift mines—also known as slant or slope mines—lie comparatively near the surface, and a roadway leads in a horizontal or inclined direction from the surface to the workings. Mines of this type are well suited for horse-haulage; they are particularly apt to become damp, because of seepage of water from the surface; and they provide easy access for rats. Jenkins and Sharp (1946) found that the risk of infection in these mines was very much greater than in deep pits served by vertical shafts.

The combined effect of these changes, in addition to rat-destruction and improvement of personal hygiene among the workers, seems to have led to a very distinct reduction in the risk of infection in coal-mines.

Sewers

The relative incidence among sewer-workers is probably much higher than among coal-miners, for Alston and Brown (1935) found leptospiral antibodies in 9 of 45 London sewer-workers, although none of them had suffered from clinical Weil's disease. In a similar examination of healthy sewer-workers in another part of London we recently found agglutinins for *L. icterohaemorrhagiae* in 3 out of 18. These also must have been the result of subclinical infections, but the large number of positive reactors indicates that the men must often come in contact with the organism.

An interesting variation in incidence among London sewer-workers occurred between 1939 and 1950. The number of cases fell sharply in 1940, and remained at a low level throughout the period of the war, but during the past few years there has again been an increase. The most likely explanation was the cessation, during the war, of any extensive repairs and renewals of sewers. This work involves the removal and replacement of brickwork and concrete, and men engaged in these tasks are prone to suffer skin abrasions. They are therefore more liable to contract the disease than "flushers," whose duties entail less manual labour.

Intensive measures for the destruction of rats were of course undertaken during the war, but were not put into force till late in 1942, and so could have played no part in the early fall in incidence. It is very regrettable that work in sewers still carries a comparatively high hazard of infection, but we may hope that the continuous campaign against rats, and also the improvement in methods of personal protection for the workers, will mitigate, if they cannot entirely eliminate, the risk.

Bathing

The risk of contracting Weil's disease while bathing in canals, rivers, and stagnant pools is well illustrated, since bathing provided the second highest total of cases. The effect of weather conditions was very marked in the hot summer of 1949, when 33 cases were reported in contrast to 15 in 1948 and 16 in 1950.

Canicola Fever

The symptoms of classical Weil's disease are too well known to need recapitulation, but the so-called "benign form," which is indistinguishable clinically from canicola fever, has received much less attention in this country. In these cases meningitis is often the outstanding feature, and the possibility of leptospirosis may never be considered in the differential diagnosis.

Clinical Aspects

Canicola fever may be taken as an example of the benign form. Table IV shows the relative frequency of various symptoms, as observed in 54 of the cases which occurred in England and Wales in the past three years. To facilitate comparison the frequencies are expressed as percentages. Since complete details are not available for every case, the totals are not all identical, and absolute numbers would give a misleading impression.

[*At this point the lecturer dealt with the symptoms and complications of canicola fever, laying particular stress on the frequency of eye affections.*]

TABLE IV.—*Symptoms in 54 Human Cases of Canicola Fever*

Symptom	%	Symptom	%
Headache	90	Albumin in urine	43
Meningitis	78	Casts in urine	14
Stiffness of neck	78	Rash	20
Injection of eyes	58	Jaundice	18
Muscle tenderness	58	Haemorrhages	16

Complete recovery is the rule, but one fatality occurred in our series, and has been fully reported (Weetch, Colquhoun, and Broom, 1949). The patient had suffered for many years from chronic nephritis, and the damaged kidneys were unable to meet the additional strain.

Only one other death from canicola fever has been recorded—in Holland (Wolff, van Dam, and Minkenhof, 1951)—and in this case also the patient was suffering from a long-standing lesion of the kidney. To avoid confusion it should be noted that the reference quoted is the first published account of the Dutch case. It was, however, mentioned by van Thiel (1948) as "the first fatal case in the Netherlands, observed by Ruys in 1947," and also by Weetch *et al.*, who give the reference as "Ruys (1947)," and state in a footnote that information about the patient had been supplied in a personal communication from Professor Charlotte Ruys and Professor Wolff.

Sex and Age Incidence

Dogs are the carriers of *L. canicola*, so the disease is a domestic rather than an occupational one. For that reason the epidemiology of canicola fever differs in many respects from Weil's disease. In this series the sex distribution was 44 males and 26 females; this is about 63% of males, as compared with 95% in Weil's disease.

The age distribution of 64 cases of canicola fever is shown in Table V, in the same age-periods as were used in Table II for Weil's disease. It will be noted that the highest incidence is among adults, as in Weil's disease. When one considers the very intimate association that often exists between dogs and small children it may seem surprising that the incidence is not much greater in the youngest age group, whereas in fact only one of our patients was under 5 years of age.

TABLE V.—*Canicola Fever: Age Incidence*

	Age in Years				Total
	Up to 15	16–30	31–45	46–60	
No. of cases	15	21	21	7	64

From inquiries into the history of our cases it seems clear that the infectivity of *L. canicola* must be low for humans. It is usual to find that only those persons in a household who have nursed a sick dog and cleaned up its dejecta have contracted the disease. We have been able to examine samples of serum from all the members of a few families in which a single human case has occurred and where the source of infection was proved to be a pet dog that had recently been ill. In all these instances the sera, except of course the patient's, gave completely negative reactions. From this it appears that close contact with infective material is an essential factor in the transmission to man.

Multiple cases did occur in some households, but it is our experience that this happens only when two or more persons share the duties of cleaning up the infective urine passed either by a sick dog or by a healthy carrier. In a recent paper, Steigner and Messerschmidt (1950) report exactly similar findings in comparable investigations.

The disease can also be contracted by bathing in contaminated water, and this appeared to be the most likely source of infection in a small number of our patients. For instance, one boy, shortly before he fell ill, had been bathing in a pool in which the carcass of a dead dog was floating.

There still remains, however, a proportion of cases in which neither the likely source of infection nor the method of transmission was discovered. Much further work will be required before all the responsible epidemiological factors are elucidated.

Seasonal Incidence

Fig 4, which has been prepared in the same way as Fig. 1, shows the monthly incidence of human cases in the upper histogram. The numbers are too small to permit any definite conclusions to be drawn, but there seems to be a tendency for infections to occur more often in the second half of the year.

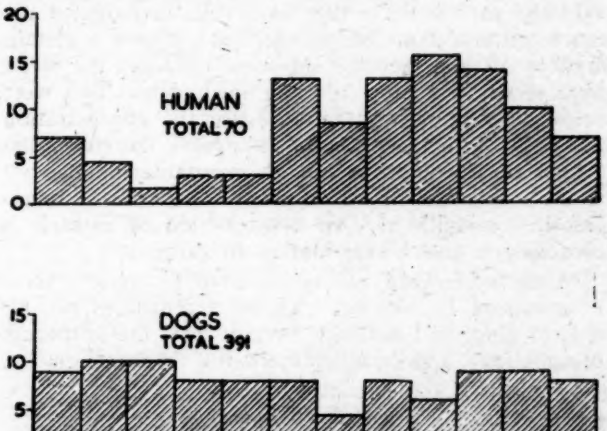

FIG. 4.—Percentage monthly incidence of canicola fever.

The incidence in dogs, represented in the lower histogram, seems to be unaffected by season. This finding differs from the opinion, held by most veterinary practitioners, that canicola fever is essentially a winter disease. That view seemed to be supported by our earlier observations (Joshua and Broom, 1949), but the results obtained then have not been confirmed as the scope of the investigations widened.

Laboratory Diagnosis

The early stages of leptospiral meningitis may simulate meningitis of tuberculous or viral origin, and a tentative diagnosis of one of these conditions is often made. It is possible that estimations of the erythrocyte sedimentation rate and the glucose content of the cerebrospinal fluid may help to discriminate among these conditions.

Erythrocyte Sedimentation Rate

Emphasis has been laid recently on the marked increase which takes place in the E.S.R. during the early stages of leptospirosis by a number of German writers (Krämer and Wieland, 1949; Scheid, 1949; Glattkowski, 1950; Litzner and Hahn, 1950; Stahl and Tetzner, 1950). From their investigations of an epidemic of field-fever Litzner and Hahn concluded that the raised E.S.R. is a constant and characteristic finding. They go so far as to say that a normal E.S.R. would in their opinion rule out a diagnosis of leptospirosis. These workers also state that the E.S.R. is normal in patients suffering from aseptic meningitis, so that this test is of diagnostic value.

Glucose Concentration in Cerebrospinal Fluid

Rubie and Mohun (1949) examined cerebrospinal fluid from a series of cases of tuberculous meningitis and found the sugar concentration to vary between 5 mg. and 45 mg. per 100 ml. The observations in leptospirosis again come almost entirely from German workers, who state that concentrations above 50 mg. are the rule. For example, Glattkowski (1950) gives details of 13 cases of canicola fever. In one patient the glucose content, which was 60 mg. per 100 ml. on the second day of disease, fell to 32 mg. on the fourth day. All the other cases showed levels of 50 mg. or more, up to the end of the second week, and nine had concentrations above 80 mg. per 100 ml.

In the past we have not, as a rule, investigated the exact concentrations of glucose, but we have a certain number of such records. In some instances the levels were above 50 mg. per 100 ml., but in others they were below that figure, and in one case the concentration was only 18 mg. per 100 ml. It appears, therefore, that a high sugar content is not an invariable finding, but if the estimation makes it possible to exclude tuberculosis meningitis in even a proportion of cases it is obviously a useful examination to carry out.

Much more work will be required to confirm these observations before they can be accepted as reliable aids to diagnosis, but they have at least the advantage of simplicity, and certainly merit full investigation.

Histological Examinations

An aid to the early diagnosis of Weil's disease might perhaps be found in the examination of biopsy specimens of muscle or of liver tissue.

Muscle Biopsy.—As long ago as 1916, Beitzke gave a good description of the degenerative changes which are found in voluntary muscles—especially the gastrocnemius. The condition affects single muscle fibres or small groups of adjacent fibres. The cytoplasm of the fibre loses its cellular detail, the striations disappear, and only fragmented masses of hyaline material remain. The adjacent unaffected portions of the fibre show no apparent alteration, and there is little or no inflammatory reaction. Sheldon (1945) carried out a series of biopsies at different stages throughout the acute attack and during convalescence, and he found that if the patient survives the fibres regenerate as a rule without fibrosis. Gardner and Wylie (1946) examined biopsy material from one patient suspected to be suffering from Weil's disease. They found the characteristic changes present some days before the agglutination test gave even an indefinite positive reaction. So far as we know, this method has not been used by any other workers up to the present.

Liver Biopsy.—In many fatal cases of Weil's disease the histological appearance of the liver seems compatible with life. Himsworth (1947) said that the essential character of the lesion will never be fully understood until a series of observations is made on biopsy material taken at different stages of the disease. Most workers have considered that the haemorrhagic tendency present in Weil's disease presents too great a hazard to the patient to justify the use of this type of investigation. Ostertag (1950), however, carried out liver biopsy in a series of 11 cases. He states that no special precautions were taken, and that no untoward incidents occurred as a result of the procedure. He found that the characteristic disorganization of the cord system and also signs of regeneration were present at an early stage, even before the appearance of jaundice.

These investigations are suggested as an aid to the early diagnosis of leptospirosis, but they cannot of course discriminate among the forms caused by different species. This can be done by isolating the strain from the blood during the first week of illness, or from the urine, where it appears towards the end of the second week. The isolation may be made by direct culture, or by the inoculation of susceptible animals and subsequent culture. In either case the identification is completed by serological tests. Alternatively, the patient's serum can be tested for the presence of leptospiral agglutinins, and the infecting species determined in this way.

Neither of these methods will provide an early diagnosis. As a rule antibodies cannot be demonstrated before the end of the first week, and in a few of our cases production was delayed for more than three weeks. It is true that leptospires can be found in the blood in the earliest stages, but five days or more must elapse before visible growth appears in cultures or, in the case of animal inoculation, before pathological effects are produced.

Thus, although these are the only two methods which provide unequivocal results, their value lies in confirming a clinical diagnosis rather than in furnishing evidence on which a diagnosis may be based or a line of treatment be indicated. It is for the latter purpose that the other techniques have been dealt with more fully, and in no wise because it is considered that they could ever supersede the well-established serological methods.

Treatment

The therapeutic use of antileptospiral serum in Weil's disease is well known, and is of proved value if treatment is begun within the first five days of illness. Early diagnosis is, however, the exception rather than the rule, unless the patient's occupation carries a known risk of infection, so most of the records refer to sewer-workers, coal-miners, or fish-cleaners.

Penicillin

Until penicillin became available none of the drugs used in the treatment of acute febrile illnesses had any curative effect in Weil's disease, although many remedies had been advocated from time to time. In animal experiments it was shown by Heilman and Herrell (1944) and by Alston and Broom (1944) that this antibiotic could prevent the appearance of symptoms in guinea-pigs, provided that treatment was begun within 24 hours of infection with *L. icterohaemorrhagiae*. These observers, however, and also Augustine, Weinman, and McAllister (1944), found the drug completely inactive if it was withheld until the animals showed signs of illness. On the other hand, Borg Petersen and Schmidt (1945) were able to cure the disease in guinea-pigs even when treatment was not begun until the fourth day after infection, and by that time the animals were manifestly sick.

Reports on the action of penicillin in human cases of Weil's disease are nevertheless often favourable. In many instances, however, this conclusion has been reached from the results in a single case or a few cases. Not infrequently, also, the drug was first administered at a comparatively late stage of illness, by which time the outcome of the attack has already been determined by the extent of the kidney damage, unless other lines of treatment are adopted.

Of those observers who have treated a number of cases, Bulmer (1945) was dealing with soldiers who contracted the disease during the summer of 1944. He states than 39 cases of Weil's disease were diagnosed, but he gives no details of the number treated with penicillin or of the results obtained. He formed the impression, however, that the antibiotic had a useful therapeutic action. On the other hand, Smith (1949), from the experience of 16 cases, thought that penicillin had little effect in toxic patients.

As compared with these small numbers, we have records of 206 cases of Weil's disease treated with penicillin in a number of hospitals in Britain during the years 1947–50 inclusive. Details of dosage and of the day of disease on which treatment was begun are, however, available for a minority only. Thirty-four of these patients died. This represents a case mortality of approximately 17%, whereas the rate for the whole series was 15%. From the crude figures it thus appears that penicillin therapy does not improve the prognosis of Weil's disease.

To compare these results with the position before penicillin was available the series reported by Broom and Alston (1948) may be used. None of the patients in the latter series received penicillin, and the death rate was 22%. It must be noted, however, that the proportion of non-icteric cases was also much lower, and, as noted above, death is very rare in the absence of jaundice. It therefore seemed that a fairer comparison would be the death rates among jaundiced

TABLE VI.—*Weil's Disease: Death Rates for Jaundiced Cases*

Description	No. of Cases	Deaths
Cases in 1947–50	263	54 (20%)
Cases treated with penicillin ..	152	34 (22%)
Cases in 1940–6	103	24 (23%)

patients. Table VI shows that the corrected case mortality for the earlier series now becomes 23%. For all jaundiced cases in the present series the rate is 20%, and for those treated with penicillin it is 22%. When the crude statistics are corrected in this manner there is still no indication of any benefit from treatment with penicillin.

These results may be analysed in another way. From the animal experiments it was evident that the curative effect of penicillin was greatest when the drug was given during the first days of illness. Suchett-Kaye (1951), recording the successful treatment with penicillin of six consecutive cases, stresses the importance of the early institution of antibiotic therapy.

We have records of 51 cases in which the day of disease on which treatment was begun is known, and the results are shown in Table VII. Thirty-six patients recovered, and for the last line of the table the number of recoveries which would be expected in each period if the drug had no beneficial action has been calculated. The probability (P) that the differences could be the

TABLE VII.—*Weil's Disease: Penicillin at Different Stages*

	Interval in Days from Onset to Treatment				Total
	1–5	6–10	11–15	Over 15	
Deaths	2	11	2	0	15
Recoveries ..	8	19	5	4	36
Recoveries expected	7·0	21·2	7·8		36

P = 0·8

result of chance is 0.8, which means that a difference as great or greater than this would be expected 8 times in 10 trials.

The conclusion must be drawn, therefore, that these patients at least obtained no benefit from the administration of penicillin at any stage of the disease.

If the general case mortality of 20% is applied to the series reported by Suchett-Kaye, a similar calculation shows that the recovery of every patient in a set of six consecutive cases could be expected to occur in approximately 5 out of 10 such sets as the result of chance alone if the treatment had no effect whatsoever.

An interesting parallel to these findings is shown by the action of penicillin in dogs infected with *L. icterohaemorrhagiae*. Joshua and Freak (1947) noted very little response to penicillin therapy, in contrast to the dramatic improvement effected by the drug in the early stages of canine canicola fever. The latter is not a fatal disease in man, so no similar comparison can be made for human infections.

In view of the results of this analysis, it is surprising to note that most clinicians report a marked improvement with penicillin treatment. Further investigations may show that in favourable cases the antibiotic speeds recovery and shortens the tedious convalescence which is so characteristic of leptospirosis.

Other Antibiotics

No report of the use of streptomycin in human leptospirosis has been published, although it was found effective in experimental infections of hamsters with *L. icterohaemorrhagiae* by Heilman, Knutson, and Greenburg (1945). In our series five patients received this drug, sometimes in conjunction with other antibiotics, and four recovered.

"Aureomycin" was used in three other cases, with two recoveries and one death. Two other patients were treated with chloramphenicol, and both died. No conclusions can be drawn from such a small number of cases, though favourable comments on the action of aureomycin have been made on the result in single cases by Lurie (1949), Brainerd *et al.* (1949), and Batchelor and Todd (1950).

Other Lines of Treatment

In fatal cases of leptospirosis death usually ensues about the 14th day, and is the result of uraemia following damage to the kidneys. The exact nature of the renal lesion is not fully understood, but it produces symptoms similar to those found in blackwater fever, incompatible blood transfusion, crush injuries, and traumatic uraemia following wounds by high explosive missiles, as described by Darmady *et al.* (1944). The kidneys in all these conditions present certain pathological features in common. The cortex is pale, and the medulla dark and engorged. Histologically the glomeruli appear relatively normal, but degenerative changes are widespread in the convoluted tubules and loops of Henle.

Darmady and his colleagues suggest that the renal failure may be due to anoxia of the kidney, possibly resulting from a period of hypotension or from neurogenic vascular disturbance. In blackwater fever, Maegraith and Findlay (1944) consider, to use their own words, "one of the more probable causes of renal failure is an alteration in the distribution of the blood flow through the kidney whereby circulation through the glomerular capillary beds is so reduced that filtration is grossly restricted." They think that the blood flow through the cortex has been mainly short-circuited into the medullary vessels, with some of the blood running direct through the cortex to the subcapsular vessels.

The renal circulation has been intensively studied by Trueta *et al.* (1947), and their investigations have shown the existence in rabbits of an alternative, intrarenal circulation through which the blood can by-pass the cortex. If such a mechanism is present in man it would offer a possible explanation of the renal failure in these conditions of such apparently varied aetiology.

Evidence in favour of this hypothesis is the re-establishment of renal function which follows paralysis of the sympathetic nerves. Robertson (1946) and Williams (1947) have successfully treated anuric cases of Weil's disease by high spinal anaesthesia, and this method has been found effective by other workers in anuria following incompatible blood transfusion. As Williams points out, it is necessary to raise and to maintain the blood pressure at a sufficiently high level to promote full urinary secretion.

Other means might be taken to tide the patient over the critical period of anuria, and to reduce the blood-urea level, until the kidneys resume their function, as they will do in time provided death can be averted. Peritoneal dialysis was used by Reid, Penfold, and Jones (1946) to relieve the uraemia in one patient suffering from anuria following incompatible blood transfusion; The artificial kidney was employed by Murray, Delorme, and Thomas (1949) in a similar case, and in two others in which uraemia followed acute sepsis.

These methods have not been tried in the treatment of Weil's disease, but exchange transfusion has been practised in one case. This technique had been carried out successfully by Dausset (1950) in 29 of 44 cases of anuria resulting either from sepsis or from the ingestion of various poisons, but it failed in this case of Weil's disease. The patient received 9 litres of blood in two days, and his condition improved for a time. Some four hours after the second transfusion, however, he collapsed suddenly, and died within a further two hours. The sudden and unexpected death was thought to be due to a transfusion incompatibility and not to the leptospiral infection.

From this rapid review it appears that these temporary expedients may sometimes at least be of great value. Reports about many more cases will, however, be required before the most effective method will emerge.

Prevention

Prophylactic measures may be designed (1) to provide personal protection; (2) to destroy leptospires; (3) to prevent contamination by carrier hosts.

Personal Protection

(*a*) *Serum.*—Injections of specific immune serum have been administered to laboratory workers who have been cut or scratched with instruments contaminated with infective material. This method has also proved effective in protecting valuable dogs which had been exposed to a high risk of infection with *L. icterohaemorrhagiae*. As a preventive measure it has, however, no general application.

(*b*) *Vaccines.*—The protection of large numbers of coal-miners in Japan against Weil's disease by the inoculation of culture vaccines of *L. icterohaemorrhagiae* was carried out by Wani (1933). Fairly severe local and general reactions were noted in a considerable proportion of the subjects, but Wani claimed that the case incidence among the vaccinated men was much lower than in control groups of unprotected miners. Smith (1937) used the method experimentally, but no other large-scale test has been made in man. A similar vaccine is extensively used for the prophylaxis of yellows in dogs, and more recently a vaccine of *L. canicola* has also been introduced. These vaccines have generally consisted of whole cultures in which the organisms were killed by phenol or formalin; but the method advocated for dogs by Meyer and Brunner (1950) of using washed suspensions of leptospires killed by freezing may provide a product which is less likely to cause severe reactions in man.

(*c*) *Protective Clothing.*—The wearing of rubber boots and gloves, which should be washed with disinfectant before being removed, would be likely to give a good measure of protection. This method would be practicable only when the number of persons at risk was small, and when work could be carried out while wearing heavy gloves. It could not be applied, for instance, in the circumstances of the epidemic of field-fever described by Popp (1950). That outbreak occurred among pea-harvesters, who are not regular agricultural workers. Some 10,000 persons were recruited annually in one district, and they were employed for a period of four to five weeks only.

(*d*) *Hygiene.*—In occupations which carry a known risk of infection, workers should clean and disinfect cuts and abrasions as soon as possible, and they should avoid practices, such as leaving scraps of food, likely to attract carrier rodents. Chang, Buckingham, and Taylor (1948) found that leptospires are rapidly killed by small concentrations of "halazone," a compound containing chlorine, and the use of a barrier cream containing this chemical has been suggested. We have carried out a few experiments with creams in which were incorporated various compounds which liberate chlorine in contact with water. The abdomen of guinea-pigs was shaved, and the skin lightly scarified. The cream was thoroughly applied over the whole area, and thereafter a single drop of a virulent culture of *L. icterohaemorrhagiae* was allowed to dry on the surface. In no case have the compounds so far tested prevented infection, but the work is being continued in the hope that an effective one may be found. By making widely known the risk of contracting Weil's disease by bathing in stagnant water, a considerable reduction in the number of cases should be achieved.

Destruction of Leptospires

Tohyama (1924) recommended the use of calcium cyanamide as a fertilizer to reduce the incidence of Weil's disease in the rice fields of Japan. The destructive effect of this material was considered by Taylor and Goyle (1931) to be due to the di-cyandiamide which it always contains, and the method would be applicable only in special circumstances.

Prevention of Contamination

(*a*) In the case of Weil's disease measures should be taken to make premises proof against rats, and continuous campaigns of rat-destruction should be carried out. Fresh-water bathing pools should also be protected, and the water chlorinated to destroy any leptospires which may gain access.

(*b*) Canicola fever presents a different problem because of the association between dogs and man. Owners of sick dogs should be warned of the chance of infection and advised to

disinfect the animal's dejecta. When a human case is diagnosed every effort should be made, by testing samples of serum in the presence of agglutinins, to trace the dog which provided the focus of infection. As has already been mentioned, it is important to bear in mind that dogs, including young untrained puppies, may be symptomless carriers.

According to Brunner and Meyer (1949), once leptospires have become established in the kidney tubules they cannot be eradicated by penicillin therapy but only by a course of treatment with streptomycin, in daily doses of 40 mg. per kg. of body weight for four days.

Summary

A short review is given of the history and classification of the genus *Leptospira*; of the distribution of different species; and of the diseases they produce in domestic animals.

An analysis of 465 cases of Weil's disease which occurred in England and Wales from 1947 to 1950 is made with regard to age, sex, occupational, and seasonal incidence, and also the incidence in different parts of the country.

Attention is drawn to the high incidence among agricultural workers and the number of infections contracted while bathing.

The suggestion is put forward that the reduced incidence in coal-miners may be due to a combination of increased mechanization, better pumping, closure of drift mines, and improved hygiene among the workers.

The symptoms most often noted in 54 cases of canicola fever are described, and some of the epidemiological differences between this infection and Weil's disease are enumerated.

The possibility is discussed of improving the early diagnosis of leptospirosis by estimating the erythrocyte sedimentation rate and the glucose concentration of the cerebrospinal fluid, and by the histological examination of biopsy material from liver and voluntary muscle.

An analysis is made of the results of treatment of 206 cases of Weil's disease with penicillin, from which it appears that the antibiotic does not reduce the death rate, irrespective of the stage of illness at which administration is begun.

A description is given of methods of prevention which are applicable in Weil's disease and canicola fever.

I should like to record my thanks to the many physicians and pathologists who have provided me with information and with material for investigation.

REFERENCE

Adam, W. (1950). *Städtehygiene*, **1**, 214.
Alston, J. M., and Broom, J. C. (1944). *British Medical Journal*, **2**, 718.
—— and Brown, H. C. (1935). Ibid., **2**, 339.
Augustine, D. L., Weinman, D., and McAllister, J. (1944). *New Engl. J. Med.*, **231**, 358.
Batchelor, T. M., and Todd, G. M. (1950). *J. Amer. med. Ass.*, **143**, 21.
Beitzke, H. (1916). *Berl. klin. Wschr.*, **53**, 188.
Borg Petersen, C. (1944). *Acta path. microbiol. scand.*, **21**, 504.
—— (1949). *Proc. roy. Soc. Med.*, **42**, 714.
—— and Schmidt, M. R. (1945). *Acta path. microbiol. scand.*, **22**, 462.
Borst, J. G. G., Ruys, A. Ch., and Wolff, J. W. (1948). *Ned. Tijdschr. Geneesk.*, **92**, 2920.
Brainerd, H., Lennette, E. H., Meiklejohn, G. Bruyn, H. B., and Clark, W. H. (1949). *J. clin. Invest.*, **28**, 992.
Broom, J. C., and Alston, J. M. (1948). *Lancet*, **2**, 96.
—— and MacIntyre, A. B. (1948). *Vet. Rec.*, **60**, 487.
Brunner, K. T., and Meyer, K. F. (1949). *Proc. Soc. exp. Biol. N.Y.*, **70**, 450.
Bulmer, E. (1945). *British Medical Journal*, **1**, 113.
Chang, S. L., Buckingham, M., and Taylor, M. P. (1948). *J. infect. Dis.*, **82**, 256.
Collier, W. A. (1948). *Acta trop., Basel*, **5**, 135.
Darmady, E. M., Siddons, A. H. M., Corson, T. C., Longton, C. D., Vitek, Z., Badenoch, A. W., and Scott, J. C. (1944). *Lancet*, **2**, 809.
Dausset, J. (1950). *Arch. intern. Med.*, **85**, 416.
Field, H. I. (1949). *Proc. roy. Soc. Med.*, **42**, 719.
—— and Sellers, K. C. (1950). *Vet. Rec.*, **62**, 311.
—— —— (1951). Ibid., **63**, 78.
Gardner, A. D., and Wylie, J. A. H. (1946). *Lancet*, **1**, 955.
Glattkowski, G. (1950). *Dtsch. med. Wschr.*, **75**, 857.
Goldschmidt, F. (1887). *Dtsch. Arch. klin. Med.*, **40**, 238.
Heilman, F. R., and Herrell, W. E. (1944). *Proc. Mayo Clin.*, **19**, 89.
—— Knutson, M., and Greenburg, N. (1945). Ibid., **20**, 169.
Himsworth, H. P. (1947). *The Liver and its Diseases*. Blackwell Scientific Publ., Oxford.
Inada, R., Ido, Y., Hoki, R., Kaneko, R., and Ito, H. (1916). *J. exp. Med.*, **23**, 377.
Jenkins, T. H., and Sharp, W. C. (1946). *British Medical Journal*, **1**, 714.
Johnson, D. W. (1942). *Med. J. Aust.*, **1**, 431.
—— (1950). Ibid., **2**, 724.
Joshua, J. O., and Broom, J. C. (1949). *Vet. Rec.*, **61**, 711.
—— and Freak, M. J. (1947). Ibid., **59**, 595.
Kathe, J. (1950). *Zbl. Bakt.* (1 Abt., Orig.), **155**, 199*.
Krämer, R., and Wieland, O. (1949). *Arztl. Forsch.*, **3**, 460.
Litzner, S., and Hahn, H. (1950). *Dtsch. med. Wschr.*, **75**, 882.
Lurie, I (1949). *Acta med. orient., Tel-Aviv*, **8**, 188.
Maegraith, B. G., and Findlay, G. M. (1944). *Lancet*, **2**, 403.
Meyer, K. F., and Brunner, K. T. (1950). *Acta trop., Basel*, **7**, 1.
Mino, P. (1938). *3rd Int. Congr. trop. Med., Amsterdam, Acta*, **1**, 422.
Murray, G., Delorme, E., and Thomas, N. (1949). *British Medical Journal*, **2**, 887.
Noguchi, H. (1917). *J. exp. Med.*, **25**, 755.
Okell, C. C., Dalling, T., and Pugh, L. P. (1925). *Vet. J.*, **81**, 3.
Ostertag, H. (1950). *Z. Hyg. InfectKr.*, **131**, 482.
Popp, L. (1950). Ibid., **131**, 575.
Reid, R., Penfold, J. B., and Jones, R. N. (1946). *Lancet*, **2**, 749.
Robertson, K. (1946). *British Medical Journal*, **2**, 810.
Rubie, J., and Mohun, A. F. (1949). Ibid., **1**, 338.
Scheid, W. (1949). *Dtsch. med. Wschr.*, **74**, 898.
Sheldon, W. H. (1945). *Arch. intern. Med.*, **75**, 119.
Smith, J. (1937). *J. Hyg., Camb.*, **37**, 261.
—— (1949). *Brit. J. industr. Med.*, **6**, 213.
Stahl, E., and Tetzner, E. (1950). *Dtsch. med. Wschr.*, **75**, 254.
Steigner, K. Fr., and Messerschmidt, T. (1950). *Z. Immun-Forsch.*, **108**, 37.
Stuart, R. D. (1946). *Vet. Rec.*, **58**, 131.
Suchett-Kaye, A. I. (1951). *Lancet*, **1**, 90.
Taylor, J., and Goyle, A. N. (1931). *Indian med. Res. Mem.*, No. 20.
Tohyama, Y. (1924). *Jap. med. Wrld*, **4**, 193.
Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Pritchard, Marjorie M. L. (1947). *Studies of the Renal Circulation*. Blackwell Scientific Publ., Oxford.
van Riel, J. (1946). *Ann. Soc. belge Méd. trop.*, **26**, 197.
van Thiel, P. H. (1948). *The Leptospiroses*. Univ. Press, Leyden.
Walch-Sorgdrager, B. (1939). *Bull. Hlth Org. L.o.N.*, **8**, 143.
Wani, H. (1933). *Z. ImmunForsch.*, **79**, 1.
Weetch, R. S., Colquhoun, H., and Broom, J. C. (1949). *Lancet*, **1**, 906.
Weil, A. (1886). *Dtsch. Arch. klin. Med.*, **39**, 209.
Williams, M. H. C. (1947). *Lancet*, **1**, 100.
Wolff, J. W., van Dam, R., and Minkenhof, J. E. (1951). Ibid., **1**, 1100.

Research in the U.S. army has developed a new foot powder to reduce foot perspiration by as much as 24%, thus offering partial protection against cold injuries to troops living or fighting in cold weather areas. The new preparation has a powdered talc base and contains aluminium chloride and potassium alum, as anhidrotic agents, as well as boric acid, salicylic acid, and starch, and the first shipment of the powder will be issued this autumn to troops assigned in cold weather areas, including those in Korea. The powder will be packaged in seven separate envelopes contained in one heat-sealed cellulose kit. This is a soldier's one-week supply. Troops will be instructed in its use. Additional research, using a combination of a rubber-barrier sock and the new foot powder, has shown a 60% reduction in perspiration. A new type rubber boot is being developed that will embody the principle of the rubber-barrier sock to eliminate the extra rubber-type sock. It will be used in combination with the foot powder. The powder is intended to be used alone where the military situation permits a daily change of socks and shoes. The secretion of the sweat glands is especially harmful in cold weather because crystallized particles of perspiration act as conductors of cold, thereby diminishing the insulative value of winter footwear. By reducing foot sweating, the new powder will decrease the risk of frost-bite —the danger of "dry-cold," just as trench-foot is the danger of "wet-cold."

FURTHER EXPERIENCES WITH PROLONGED TREATMENT OF RHEUMATOID ARTHRITIS WITH A.C.T.H. AND WITH GOLD*

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In an earlier report several problems concerning the long-term treatment of rheumatoid arthritis with A.C.T.H.‡ were discussed (Goslings *et al.*, 1950). Since that time relatively few authors have concerned themselves with this subject (Hench *et al.*, 1950; Boland, 1950). The conclusion reached from their work is that the general application of A.C.T.H. for the routine treatment of rheumatoid arthritis is not yet justified.

The investigations carried out at this centre on patients receiving prolonged treatment with A.C.T.H. have of late met with special difficulties in a group of patients who originally responded to therapy but later entered into what might be termed a refractory state. In this article several possible explanations of that failure are discussed.

Materials and Methods

The selection of patients was the same as that indicated in a previous communication. All patients were in hospital during the whole course of treatment and received the benefit of general symptomatic and physical therapy. Simultaneous treatment with gold was given during at least part of the A.C.T.H. therapy. Only patients who had failed to respond to gold therapy at an earlier stage of their disease, or who had received no previous treatment, were included in the series.

The methods used have been reported elsewhere (Querido *et al.*, 1951). The estimation of the excretion of the formaldehydogenic corticoids has been adapted from Daughaday's method (Daughaday, Jaffe, and Williams, 1948) as modified by Mason (personal communication, 1950). The ascorbic acid content of the urine was measured by titration with 2,6-dichlorophenolindophenol at *p*H 4.1. The classification of the rheumatoid process and the assessment of results have been adopted from the therapeutic criteria outlined by Steinbrocker *et al.* (1949).

Results

Table I gives the total number of patients included in this study, their period of treatment, time of follow-up, and the maximal and minimal amounts of A.C.T.H. administered per patient.

TABLE I.—*Details of Patients Treated*

Number	20
Period of A.C.T.H. administration	1½–8 months
Follow-up after discontinuation of A.C.T.H.	1–14 months
Amount of A.C.T.H. per patient	1,150–6,570 mg

Two conclusions may be drawn from an analysis of the results of treatment with A.C.T.H. (Table II).

TABLE II.—*Results of Treatment with A.C.T.H.*

Result	Optimal Condition	Present Condition
Deterioration	0	3
No improvement	0	7
Minor improvement	3	4
Major improvement	6	5
Complete remission	11	1
Total	20	20

(1) Complete Remission not Always Obtained

It seems justifiable to suppose that a higher daily dosage might have improved these results. That 100% improvement cannot always be expected, however, is shown by the following case. One patient received six doses of 15 mg. a day without a total disappearance of signs and symptoms, in spite of a marked response with regard to the excretion of 17-ketosteroids. In this connexion it is considered important, when comparing the effects of different daily dosages of A.C.T.H., to state the number of injections daily as well as the total amount administered, divided doses producing a greater adrenal response than single ones (Querido *et al.*, 1951).

(2) Effect Maintained in a Relatively Small Minority of Cases

Deterioration occurred not only after the cessation of therapy but in the latter part of this study during the administration of the hormone in a dosage which was considered sufficient for an adequate adrenal response. Earlier experience had given an indication of the minimal effective dosage in six patients. In three this was found to be six doses of 2 mg. a day, these patients relapsing on six 1-mg. doses a day. Remission was sustained in a fourth patient with six 2-mg. doses daily. The two remaining patients required larger doses, but both had complicating diseases (nephrotic syndrome, psoriasis).

In sharp contrast with these results, the last patient of the series (No. 20, see below) relapsed in spite of a continued schedule of six doses of 7 mg. daily.

As a detailed description of the case histories would not assist in assessing the problems of long-term administration of the hormone, the most important facts are summarized in Table III.

So far, no correlation can be found between the severity of the disease and the results of therapy, nor between the maintenance of improvement and the total amount of A.C.T.H. given.

Illustrative Cases

In illustration of these divergent and often disappointing effects, the relevant data of two cases are presented. The first is an example of a highly satisfactory clinical response with sustained remission during prolonged low-dosage administration of A.C.T.H. The second demonstrates a complete relapse during the fourth week of treatment with A.C.T.H.

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‡Unless otherwise stated, the pituitary hormone used throughout these studies was "cortrophine" (Organon). The dosages used are expressed in mg. Organon standard, which is equivalent to the provisional international A.C.T.H. standard.

TABLE III.—*Results of A.C.T.H. and Gold on 20 Patients with Rheumatoid Arthritis*

Case	Sex	Age	Duration of Disease Before A.C.T.H.	Stage of Disease	Functional Impairment	Duration of Administration of A.C.T.H.	Total Amount Administered in mg.	Degree of Improvement During Period of Optimal Condition	Degree of Improvement at End of A.C.T.H. Therapy	Period of Follow-up After A.C.T.H.	Degree of Improvement at the End of Follow-up Period
1 Sch.	F	36	7 yrs.	III	III	138 days	1,960	Complete	Complete	14 mths.	None‖
2 Swa.	M	42	10 ,,	IV	IV	102 ,,	3,170	Minor	None	4 ,,	+ Cachexia
3 Lis.	F	33	12 ,,	III	II	120 ,,	1,839	Complete	Complete	14 ,,	Major
4 Dri.	M	65	7 ,,	IV	IV	118 ,,	2,625	Minor	Minor	1 mth.	+ Uraemic
5 Gri.*	F	56	1½ ,,	II	III	66 ,,	1,194	Complete	Complete	5 mths.	Major
6 Rij.†	M	32	2½ ,,	IV	III	175 ,,	2,042	,,	Major	14 ,,	,,
7 Mas.	F	54	6 ,,	III	III	166 ,,	2,608	,,	Complete	6 ,,	,,
8 Pol.	M	50	1½ ,,	II	III	110 ,,	1,839	Major	Major	7 ,, ‡	None
9 Har.	F	28	6 ,,	II	II	247 ,,	4,535	Complete	Deterioration	Cortisone	
10 Dij.	F	37	10 ,,	III	IV	135 ,,	1,692	Major	Major	8 mths.	Major
11 Bos.	F	48	15 ,,	IV	IV	90 ,,	1,512	Minor	None	7½ mths.	Minor
12 Li.*	F	46	6 mths.	I	III	144 ,,	2,285	Complete	Complete	4½ ,, ‡	Complete
13 Me.	F	29	10 yrs.	III	IV	176 ,,	6,570	Major	None	Cortisone‡	
14 Her.	F	40	4 ,,	III	II	73 ,,	2,146	Complete	,,	,,‡	
15 Hen.	F	50	8 ,,	III	IV	103 ,,	2,390	,,	,,	,,‡	
16 Lat.	F	29	7 mths.	II	IV	127 ,,	2,284	Major	Minor	,,‡	
17 Lud.	M	59	1 yr.	II	III	55 ,,	2,123	Complete	,,	,,‡	
18 Be.	M	55	3 mths.	III	IV	52 ,,	1,346	,,	Deterioration	6 weeks	Deterioration
19 Lef.	F	43	7 yrs.	III	IV	89 ,,	1,959	Major	Minor	A.C.T.H.§	
20 Ran.	F	50	11 ,,	II	III	55 ,,	2,130	,,	Deterioration	3 weeks	,,

* No previous therapy. † Ankylosing spondylitis, afterwards treated with amidopyrine. ‡ Now treated with cortisone. § Still on A.C.T.H. therapy. ‖Relapse occurred 10 months after discontinuation of A.C.T.H.

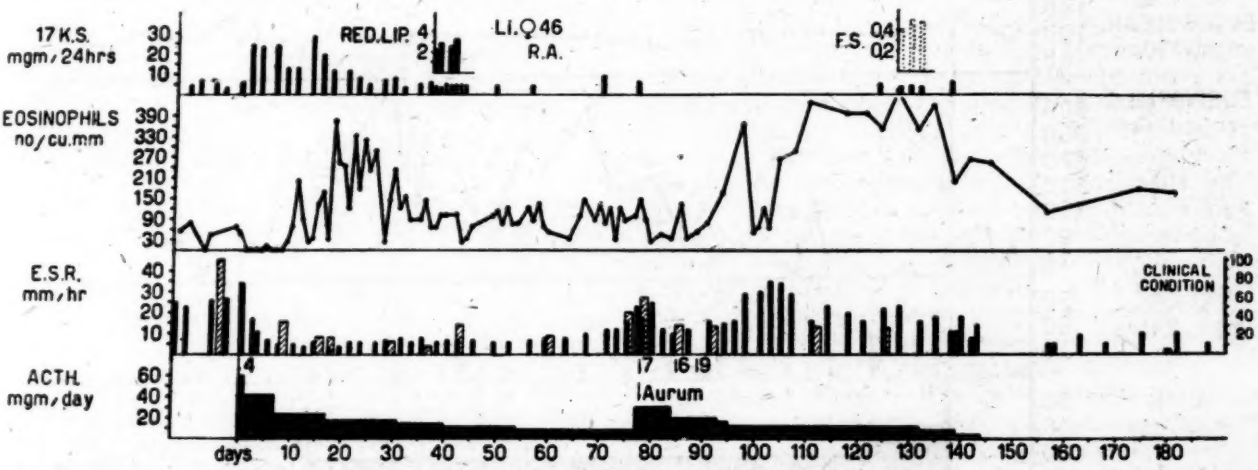

FIG. 1.—Case 12. Sustained remission after A.C.T.H. therapy, combined with gold treatment. Red. Lip.=reducing lipids. F.S.=formaldehydogenic steroids. ⌊Aurum=chrysotherapy started. The numbers in the lowest column refer to the batches of cortrophine used. The hatched areas represent the clinical condition of the patient, expressed in percentages of the pretreatment level (=100%).

Case 12 (Fig. 1).—A housewife 46 years old was admitted to hospital because of rheumatoid arthritis of six months' duration. The *x*-ray films of the affected joints were still normal, and no irreversible deformities had then developed. An attempt was made to arrest the active process at an early stage, and the normal course of treatment was begun. This consisted of six 7-mg. doses of A.C.T.H. daily until signs and symptoms had subsided, followed by a gradual reduction in dosage, first by decreasing the amount given at each injection and later by reducing the number of injections daily. A good adrenal and clinical response resulted. After a week, eosinophils reappeared in the peripheral blood without a change in the patient's condition. During the next nine weeks the patient remained in an excellent condition. On the seventy-fifth day she relapsed, the dosage at that moment being three 3-mg. doses daily. This demonstrates that A.C.T.H. alone was unable to produce a lasting remission in a case of recent origin.

A major improvement occurred when the daily dosage was raised to five of 6 mg., at which time gold therapy was begun. A temporary increase in the E.S.R. was observed from the ninety-fifth day of treatment onwards, probably due to the chrysotherapy. Such a phenomenon is often observed during the first weeks of this form of therapy. Four months after the last A.C.T.H. injection she was free from symptoms, the E.S.R. being 5–15 mm. (Westergren).

Case 18 (Fig. 2).—A business manager, 55 years old, was also suffering from rheumatoid arthritis of recent origin. Most of his peripheral joints were affected, his sedimentation rate was constantly higher than 100 mm., and his temperature fluctuated between 37.5° C. and 38.5° C. The severity of the process can be judged from the fact that during the three months of his illness distinct atrophy of his thenar muscles and ulnar deviation of the metacarpo-phalangeal joints had developed. His improvement was the most dramatic in the whole series of A.C.T.H.-treated patients. After four and a half weeks of therapy, however, when six doses of 4 mg. had been given daily for two and a half weeks, a total relapse occurred.

Discussion

It is always difficult to assess the results of therapy in a chronic illness with an irregular and changing course, such as rheumatoid arthritis. The literature makes it clear that 100% successes are never found with A.C.T.H. or cortisone. These considerations may partly

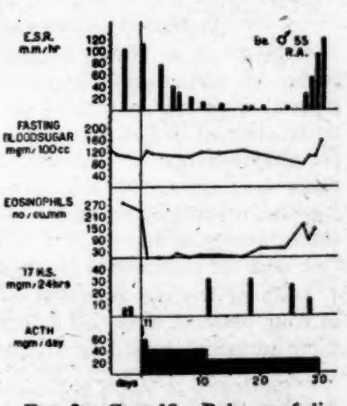

FIG. 2.—Case 18. Relapse of disease in fourth week of A.C.T.H. therapy. By that time the patient had received six doses of 4 mg. for a fortnight.

explain the variation in clinical response and the differences in dosages required, but cannot entirely account for the fact that, of late, patients constantly relapse after four to seven weeks' administration of the hormone, having initially shown satisfactory improvement. Below, attempts are made to account for the failures.

(a) Diminished Response to Cortisone-like Substances

One reason for failure may be a diminished response of the peripheral target organs to the cortisone-like substances produced by the adrenals under the influence of exogenous A.C.T.H. To test this hypothesis six patients who had become refractory to A.C.T.H.* were given cortisone in normal quantities—for example, 200 mg. on the first day, 150 mg. on the second, and 100 mg. daily until at least a major improvement was obtained, followed by 50 to 75 mg. a day. All six responded favourably to this scheme of treatment. Case 15 is representative of this group (Fig. 3). In these cases a diminished response of the periphery could be excluded.

TABLE IV

	I^{131}% Excretion After				Total I^{131} Excretion in 48 hrs.
	0–8 hrs.	8–12 hrs.	12–24 hrs.	24–48 hrs.	
♀Her. (Case 14)	42·1	8·5	8·0	2·4	61·0
♀Hen. (Case 15)	25·5	6·1	2·7	1·1	35 4
♀Har. (Case 9)	45·6	6·5	5·4	1·5	59·0
♀Me. (Case 13)	39·8	5·1	11·9	3·2	60·0
♀Normal figures	27–44	4·4–10	3·8–11·6	1·7–9·4	49·5–62
Hypothyroidism			11–18	18–23	60–90

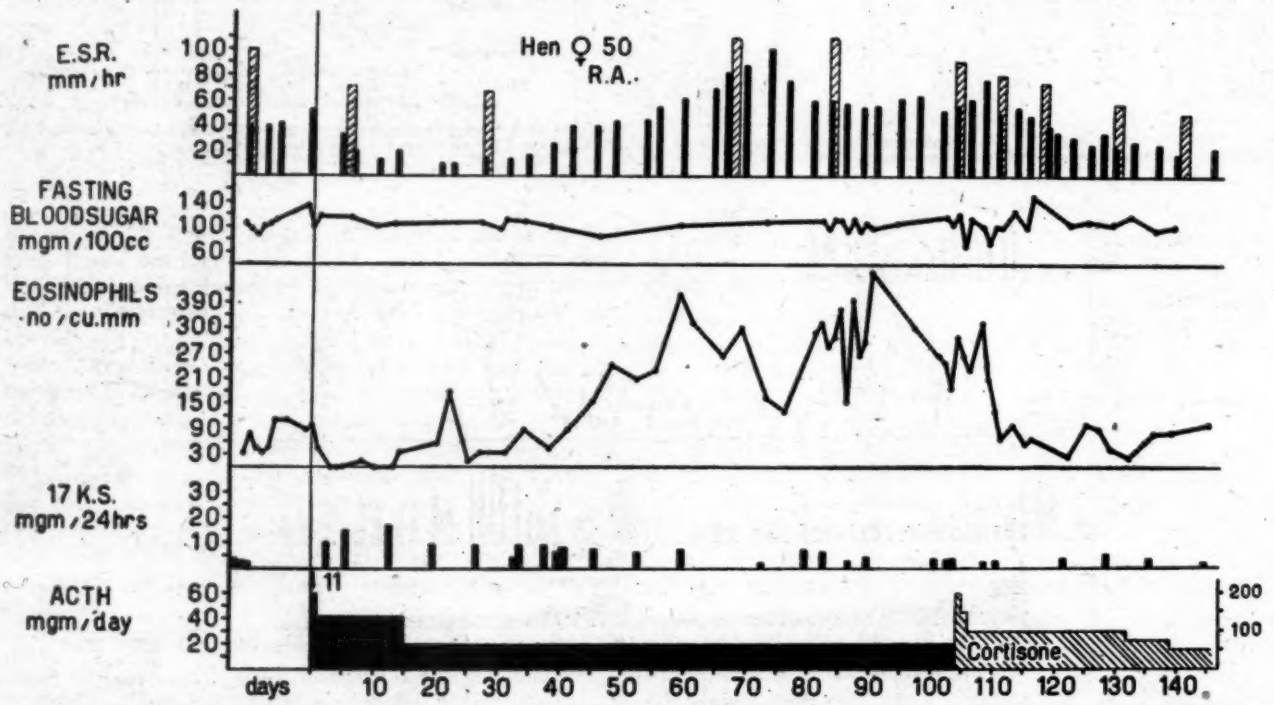

FIG. 3.—Case 15. Development of refractory state to A.C.T.H. after initial period of improvement. Satisfactory clinical reaction to usual amount of cortisone, indicating responsiveness of peripheral target-organs.

(b) Masked Corticogenic Hypothyroidism

Wolfson *et al.* (1950) suggest that the "possible existence of corticogenic hypothyroidism should be considered whenever a patient ceases to respond well to a daily dose of A.C.T.H. which previously was adequate for maintenance." This myxoedematous state can be discovered only with the help of the newer techniques for the investigation of thyroid deficiency, because of the opposing action of A.C.T.H. on the basal metabolic rate and the cholesterol level of the blood.

Tests of thyroid function with I^{131} were carried out in four patients who had failed to respond satisfactorily after an initial period of improvement on A.C.T.H. The figures in Table IV prove that all four patients examined have a normal excretion pattern of I^{131} (Arnott *et al.*, 1949).

There is thus no evidence from these cases that the second hypothesis is correct.

(c) Failure of the Adrenals to Respond Adequately to the Corticotrophic Hormone

It is difficult to define what must be regarded as an adequate response. Has this to be judged by the satisfactory clinical effect or by the increased adreno-cortical activity according to laboratory data (fasting blood sugar, eosinophils, excretion of 17-ketosteroids and corticoids)?

Is a correlation between these two criteria obligatory or is one of them sufficient? Another difficulty is that present methods are insufficient to give an insight into the essential reactions of the adrenals to A.C.T.H.; qualitatively as well as quantitatively, the analyses of the adrenal response fail to meet the demands.

As this study has been concentrated on low-dosage schemes from the start, it has repeatedly been observed that during periods of low dosage the various laboratory criteria for adreno-cortical activity fail to indicate a positive response to the pituitary hormone used, with persistence of the clinical improvement (Fig. 1, second month of treatment). After discontinuation of this small maintenance dose a relapse may occur. On the other hand, the laboratory data in a few instances have

*"Refractory to A.C.T.H." indicates that a patient's clinical condition deteriorated in spite of the administration of a dosage which had previously caused improvement and/or maintained this improved condition. In this situation it might be possible to bring about a favourable response with higher doses. "Relatively refractory" might be a more appropriate description.

indicated a quantitatively satisfactory response, whereas the patients have shown unmistakable signs and symptoms of the recurrence of the disease. One example (Case 20) is given graphically in Fig. 4.

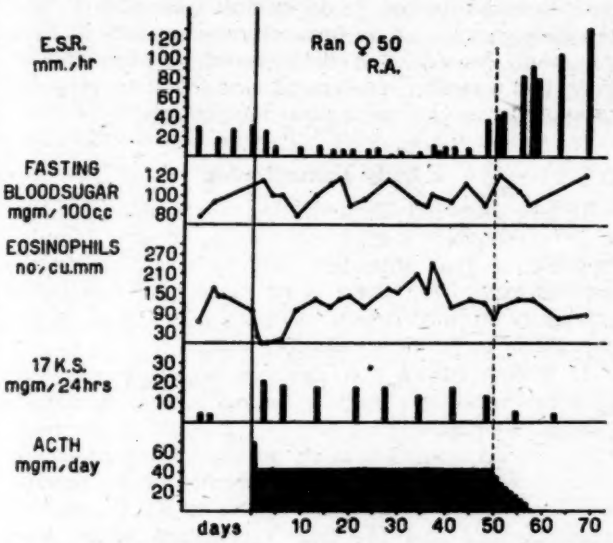

FIG. 4.—Case 20. Relapse of disease in eighth week of A.C.T.H. therapy, in spite of six doses of 7 mg. daily.

This 50-year-old schoolteacher had been in the rheumatism wards for more than a year. She reacted only partially to routine therapy. For seven weeks she received six doses of 7 mg. daily. She relapsed on the forty-eighth day of treatment, and after a few days was worse than before the initiation of A.C.T.H. therapy. At the time of her relapse the excretion of 17-ketosteroids was 13.4 mg., compared with a pre-treatment level of 4.2 and 4.6 mg. per 24 hours. It is obvious that there is no correlation between the clinical and laboratory criteria. It is possible that laboratory methods which give a more thorough analysis of the adrenal response would indicate a shift in the hormone production and show a relative insufficiency.

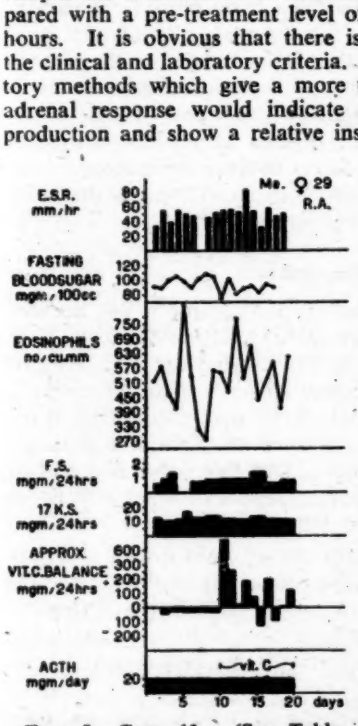

FIG. 5.—Case 13. (See Table III.) During the 10-day period indicated, a daily amount of 1 g. of ascorbic acid was administered intravenously. The vitamin C content of the diet was kept as low as possible by eliminating fresh fruit and vegetables. No effect was observed on the criteria of adrenocortical activity or on the clinical condition.

At the moment we are unable to come to a conclusion regarding this possibility.

It is known that stress and exogenous A.C.T.H. cause an ascorbic acid depletion of the adrenals; the most widely used assay for pituitary adrenocorticotrophic hormone is based on this observation (Sayers *et al.*, 1948). It might be supposed that long-continued treatment with A.C.T.H. might lead to ascorbic acid deficiency, and that this deficiency was the cause of the diminished response. If this assumption were correct extra supplies of vitamin C should enable the adrenals to react normally again. Unfortunately, experiments made in this direction lead to entirely negative results. There was no sign of increased adreno-cortical activity or clinical effect in spite of the intravenous administration of 1 g. of ascorbic acid daily (Fig. 5).

During these studies literature pertinent to this possibility appeared (Hyman *et al.*, 1950; Treager *et al.*, 1950), indicating that even in clinical scurvy there is an adequate adrenal response to A.C.T.H.

(d) Decreased Activity of the Adrenocorticotrophic Hormone

Different batches may vary in therapeutic activity in spite of an almost identical assay, which, being biological, is subject to certain variability. A few patients were therefore treated with one batch, and during a relapse this was replaced with the same amount of a Danish preparation of A.C.T.H. (Roskilde) or in one patient A.C.T.H. (Armour), for a period of six days. Daily examination of the eosinophils, fasting blood sugar, excretion of 17-ketosteroids, sedimentation rate, and clinical condition lent no support to the supposition that the cortrophine preparation had diminished in potency.

The one and a half years' study has emphasized the similarity of the therapeutic response of all the different batches of A.C.T.H. used during the initial period of treatment. However, with the batches which are available at present it appears impossible to maintain with reduced dosage the improvement brought about by the higher initial dosage, as was possible in the first group of patients. A relapse is now found to occur with less or even without reduction of the dosage, but it is presumably of greater significance that this relapse always occurs after four to seven weeks of treatment, more or less independently of the dosage used (see Figs. 2 and 4).

One patient, however, who was treated in the later period of this investigation, sustained a remission during prolonged therapy with low doses. It seems worth noting that she had received one of the old batches of A.C.T.H. which had been used in the earlier studies. Her case history has been mentioned above (Case 12, Fig. 1).

These observations suggest the possibility of the development of neutralizing antibodies against the particular batches of pituitary hormone which have been available during the last months.

Recent literature reveals that others have encountered similar difficulties. The experiences of Wolfson *et al.* (1950) have already been mentioned. Margolis and Caplan (1951), in a review of their results of prolonged treatment with A.C.T.H., describe the normal variation of the direct effect of the agent. They also mention a deterioration in the degree of improvement with long-continued administration of A.C.T.H.

Summary

Twenty patients with rheumatoid arthritis have been treated with A.C.T.H. during periods of one and a half to eight months. Invariably a relapse occurred when the administration of A.C.T.H. was discontinued or when the dosage was too low. In a few cases the improvement obtained with A.C.T.H. could be maintained by concomitant chrysotherapy.

A previous report from this centre gave the first results of A.C.T.H. therapy in rheumatoid arthritis. In four cases the minimal effective dosage was found to be six doses of 2 mg. daily.

In a group of patients studied since then an initial period of striking improvement has been followed by the onset of

a refractory state. This failure of adequate response is not only seen with low dosage but may develop in spite of continued high initial dosage, usually appearing after four to eight weeks of treatment.

Attempts to explain these failures have so far been unsuccessful. The following possibilities have been excluded by special study: masked corticogenic hypothyroidism; diminished response of the peripheral target-organs; vitamin C deficiency; and decreased activity of the pituitary hormone preparations.

Investigations into the possible development of neutralizing antibodies or a shift in the hormone production of the adrenals appear to be indicated.

The administration of A.C.T.H. in cases of rheumatoid arthritis should still be regarded as worthy of investigation.

REFERENCES

Arnott, D. G., Emery, E. W., Fraser, R., and Hobson, Q. J. G. (1949). *Lancet*, **2**, 460.
Boland, E. W. (1950). *Calif. Med.*, **72**, 405.
Daughaday, W. H., Jaffe, H., and Williams, R. H. (1948). *J. clin. Endocrinol.*, **8**, 166.
Goslings, J., Hijmans, W., v. Limpt, P. M., and v. Gilse, H. A. (1950). *British Medical Journal*, **2**, 1019.
Hench, P. S., Slocumb, C. H., Polley, H. F., and Kendall, E. C. (1950). *J. Amer. med. Ass.*, **144**, 1327.
Hyman, G. A., Ragan, Ch., and Turner, J. C. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 470.
Margolis, H. M., and Caplan, P. S. (1951). *J. Amer. med. Ass.*, **145**, 382.
Querido, A., Kassenaar, A., Goslings, J., and Hijmans, W. (1951). *Acta endocrinol.*, **6**, 90.
Sayers, M. A., Sayers, G., and Woodbury, L. A. (1948). *Endocrinology*, **42**, 379.
Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.
Treager, H. S., Gabuzda, G. J., Zamcheck, N., and Davidson, Ch. S. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 517.
Wolfson, W. Q., Beierwaltes, W. H., Robinson, W. D., Duff, I. F., Jones, J. R., Knorpp, Ch. T., and Eya, M. (1950). *J. Lab. clin. Med.* (Abstracts), **36**, 1005.

B.C.G. VACCINATION IN THE NEWBORN

PRELIMINARY REPORT

BY

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No one can rest satisfied with the results of treating tuberculous meningitis with streptomycin. Even the best figures so far reported show a mortality of some 40–50% (Debré *et al.*, 1949; Smith and Vollum, 1950). The residua, too, in the recovered cases are by no means negligible.

Tuberculous meningitis takes its heaviest toll in the early months of life—that is, in the first two years, when the chances of close contact with heavy and often continual exposure are maximal and the source of such contact is all too often undiagnosed till it is too late to save the infant.

Because of the enormous number of people with active tuberculosis at large—140,000 in England and Wales, according to a recent report (Heaf, 1950)—the risk of infants' being exposed and contracting the disease is a very real one. Indeed, guaranteed freedom from exposure is virtually impossible, and it would seem, therefore, that active immunization offers the greatest hope of success in abolishing tuberculous meningitis in infancy. Such an immunization would protect simultaneously against bovine tuberculosis, and thus the risk of infection from imperfectly treated milk would also be removed.

It has for long been held that newborn infants do not react to immunization, or do so most inadequately; and on these grounds active immunization procedures have commonly been delayed till the fourth month of life or later, and a similar recommendation might be expected to apply to vaccination against tuberculosis.

Early Immunization

If any proposed immunization programme is to be fully satisfactory it must start as soon after birth as possible, so that protection may be given against the earliest exposure. There is no placentally transferred immunity to tuberculosis as there is, or may be, to diphtheria in the early months of life.

It is now known that newborn infants can and do respond reasonably well to immunization, though in general their powers of antibody production are probably less than they are at six months of age and thereafter. Wallgren (1950) has commented on the remarkable insensitivity of newborn infants to B.C.G., and has recommended that for their vaccination larger doses should be given (twice the adult dose) and that the development of tuberculin sensitivity should not be expected till a longer time afterwards (10–12 weeks, as against 4–6 weeks in childhood).

Where segregation of the infant is necessary because of a tuberculous *milieu* in the home to which he would return, it is obviously desirable for administrative reasons, if for no other, that the period of segregation should be as short as possible. Any place of isolation, whether it be a cubicle in a hospital, a residential nursery, or a foster-home, should be free from the risk of exposure of the infant to any cross-infection, for manifestly it would militate against the success of any immunization regime if, in the process of protection against tuberculosis, death were to result from some intercurrent infection. The minimal period of isolation is therefore a matter of some practical importance.

Procedure

As part of the child health programme it was decided to immunize infants born in St. Mary's Maternity Hospital, Manchester, with B.C.G. during the first week of life. All parents are invited to have their infants thus immunized; approximately 50% avail themselves of the offer. The aim of this project is the abolition of tuberculous meningitis in infancy, and this paper is therefore obviously only a preliminary report of what will be, in the first place, a five-year follow-up study.

Attached to the department of child health is a welfare centre, open daily, to which any mother delivered at St. Mary's Hospital, or on the district, may bring her infant. It is thus hoped to be able to follow closely and at frequent and regular intervals the progress of immunized infants.

The immediate questions to which answers were desired were: (*a*) What dose of B.C.G. is necessary for effective vaccination in the newborn? (*b*) What is the minimal time in which conversion can occur? (*c*) What are the dangers of overdosage if it be found that the answer to (*b*) varies with the dose of vaccine given? (*d*) In the event of complications, what is the best treatment for them?

Intermediate problems to be studied are the duration of tuberculin sensitivity in infants vaccinated at birth; whether this varies with the type of vaccine used or with the dose injected; the number of revaccinations that will be required; and the proportion of immunized infants known to be in contact with open tuberculosis: these infants will of course receive close attention, as they comprise the group for which this study is basically aimed—the group from which our cases of tuberculous meningitis would otherwise have come.

A further study is concerned with the value of B.C.G. tuberculin for conversion testing. Magnusson and Lithander (1949) have shown that the reaction with this tuberculin may become positive some days before the old-tuberculin Mantoux test will. In all cases in which the B.C.G. tuberculin test is positive the O.T. test will also become positive; it may therefore be assumed that the homospecific allergy develops earlier. If the development of this allergy coincides with an increase in resistance to infection by human tubercle bacilli the use of B.C.G. tuberculin may prove of great value in further lessening the period of segregation necessary.

The Vaccine

Two forms of vaccine were used. One was the standard Ministry of Health vaccine delivered weekly from Copenhagen, and the other was a freeze-dried preparation made at the Pasteur Institute in Paris. The obvious advantage of the freeze-dried preparation (apart from its keeping properties) is that its strength may be altered at will by varying the volume of water in which it is dissolved without increasing the total amount injected.

All vaccinations were done intradermally, and in newborn infants 0.2 ml. is about the maximal amount that can be given in a single injection by this route. Initially we followed Wallgren's recommended dose and injected 0.2 ml. into the outer aspect of the thigh. Later we gave the injection in divided doses of 0.1 ml. about ¼ in. (0.6 cm.) apart from one another or used both thighs, giving 0.1 ml. into each. After encountering some complications we changed the site of inoculation and used the skin over the deltoid, giving 0.2 ml. as a single injection or as two injections of 0.1 ml. close to one another or one on each arm. Still later we found that 0.15 ml. was adequate to produce conversion, and finally that 0.1 ml.—the ordinary adult dose—was equally effective.

With the freeze-dried preparation the maximal dose given was 0.375 mg. in 0.2 ml., the standard strength recommended being 0.1 mg. in 0.1 ml.; but we now recommend 0.2 mg. in 0.1 ml. as the routine dose.

Results

Of the 1,461 newborn infants vaccinated to date 1,015 have completed their course and undergone Mantoux conversion. The shortest conversion time has been 16 days. All those tested have been converted within 10 weeks. In a few instances return for Mantoux testing has been delayed—in one for as long as 31 weeks. All such cases were found to be positive. With the freeze-dried vaccine the earliest conversion was on the 17th day, and the longest conversion period was 17 weeks.

For post-vaccination tests the strength of tuberculin used never exceeded 0.1 ml. of 1/100 O.T., and a large number of infants reacted to 1/1,000. The strength used varied according to the extent of the reaction at the vaccination site. Infants showing pustule formation generally react to 1/1,000; if only a small papule is evident at the primary site 1/100 dilution will probably be necessary to evoke a positive response.

There is little doubt that the time taken for allergy to develop (conversion time) does vary with the dose given. If, therefore, early conversion is imperative, larger doses must be used.

Reactions and Complications

As it is impossible to tell beforehand what sort of reaction any infant will have to the vaccine it is impracticable to vary each individual dose. Some will react more violently than others, and such reactions may be focal (that is, at the site of injection) or regional (that is, in the gland draining the area of injection). No specific systemic reactions of any kind have been encountered.

Ulceration, often very slight, has occurred at the focal site in a great many cases, but this has depended not on the size of the dose alone but also on the individual sensitivity of the infant. The reaction appears to be unrelated to the site of injection, for where the arm has been used (as is our present practice exclusively) focal reactions are just as frequent as in the thigh.

With regard to regional gland involvement, this is at first sight a more disturbing problem, particularly when fluctuation is present. It should be understood that the glands are "physiologically" enlarged in every case of B.C.G. inoculation, as they are in natural tuberculous infection, and that in infancy, and throughout childhood generally, the lymphatic involvement is always more marked than the reaction at the primary focus. Careful search, therefore, will reveal palpable enlargement in a great many cases. In the present series small glands 1–5 mm. in diameter were found in the axilla in about half the cases inoculated in the arm, and a similar enlargement was almost universally present in the inguinal glands in the cases inoculated in the thigh.

FIG. 1.—Marked inguinal adenitis with fluctuations following vaccination in right thigh—0.2 ml.—three months previously. Gland aspirated subsequently, with rapid recovery.

FIG. 2—Abscess at site of primary inoculation in right arm. Aspirated once, with streptomycin replacement. Subsequently healed rapidly—no axillary adenitis.

Fluctuation or actual breaking-down of a gland has been seen 50 times—47 times in the inguinal region and three times in the axilla. All these cases had received 0.2 ml. at a single site. Because of the frequency of this complication the thigh injections were abandoned. The probable explanation is that in infancy the inguinal glands are more active than the axillary, having continually to cope with the prepuce, vulva, and napkin areas, and that the sudden influx of a number of tubercle bacilli causes them to "blow up," whereas the comparatively quiescent axillary glands can cope successfully with the new invasion.

The high incidence of this complication which we encountered was undoubtedly due in the main to the large doses we used, particularly in the earliest stages of this study, when we were trying to determine the quickest possible conversion time. Since using the arms and giving the standard dose of 0.1 ml. no further cases have occurred, but an occasional case may still be expected, as suppurative axillary adenitis has been observed by Rekling (1945) at the Finsen Institute, Copenhagen. He reported 20 cases.

On rare occasions the axillary glands are, or seem to be, by-passed and the primary complex completed by the supraclavicular or infraclavicular gland. Palpation of this area is therefore advisable before concluding that there is no glandular reaction.

It also seems that it may be possible for a deep iliac adenitis to occur. One case, that of a baby who had received 0.2 ml. in the right thigh, was admitted to another hospital where an operation was performed for intestinal obstruction due to a band of adhesions from a mass of glands in the right iliac region. Unfortunately no gland was removed for biopsy, but it is certainly more than possible that these glands were secondary to the B.C.G. inoculation.

A case of pyloric stenosis has been reported following oral vaccination, in which pressure from mesenteric glands led to narrowing of the pyloric lumen (Ustvedt, 1951). Iliac and mesenteric glands may, however, be inflamed from other causes, and it is impossible to state dogmatically that these cases were solely B.C.G. reactions even though it is highly probable. Similarly, enlarged hilar glands may be found to follow B.C.G. inoculations in the arm, but their exact relationship to the inoculation remains unproved. None of the infants with abscesses were upset systemically; fever, anorexia, and weight loss (or failure to gain) were not noted, and secondary infection did not occur in any case.

In answer to the question which parents often ask—"Is this vaccination harmless to newborn infants?"—the answer is that, generally speaking, it is harmless, but the case of intestinal obstruction shows that there may on very rare occasions be complications of a harmful nature.

The fact which emerges is that it is possible, using large doses, to immunize a newborn infant in less than three weeks. This may be a matter of some importance in the case, for example, of an infant with a mother suffering from active tuberculosis or where there is great pressure on "preventorial" accommodation.

The fact that large doses, certainly if injected at a single site, add to the risk of complications has suggested that where early conversion is important the dose should be given in small quantities at different sites. The problem to be studied is whether the adenitis is related to the total number of organisms draining into a particular gland or group of glands or whether the bacillaemia which follows inoculation is also a factor in determining the localization of the adenitis.

Treatment of Complications

In dealing with the complications it should be borne in mind that they are without systemic danger and will heal spontaneously in time (weeks or months) even without treatment, and they have by no means the same significance as the cold abscesses of ordinarily acquired tuberculosis. Heroic measures, therefore, are not called for in dealing with these "Calmette abscesses."

Local application of a sulphathiazole powder containing 10% of streptomycin is of value, and, in the case of a fluctuant swelling, aspiration and replacement with 10,000 to 20,000 units of streptomycin may considerably expedite the subsidence. We have given P.A.S. for short periods to infants with marked glandular involvement, but do not feel that systemic streptomycin is indicated.

It must be remembered that as the adenitis may not become evident for some weeks after the post-vaccination Mantoux test has been done regular follow-up is necessary. It has happened on a few occasions that an infant has been taken to another hospital and fomentations or penicillin injections, or even surgical intervention undertaken. In an endeavour to prevent the repetition of this every mother is given a card after the successful vaccination of her infant and instructed to show it to her doctor, who may be made aware of the preceding vaccination and of the resulting positive tuberculin test.

Summary

It is both possible and practicable to immunize newborn infants with B.C.G.

They react to 0.1 ml. of vaccine as do older children and adults. For routine immunization larger doses are unnecessary, and are apt to produce complications.

The time taken for allergy to develop may be appreciably diminished by increasing the dose used.

Although complications are not generally harmful they are nevertheless undesirable, and the effort to secure a minimal conversion time should be restricted to selected infants for whose special circumstances the time factor is of great importance.

It is suggested that in such circumstances complications may be prevented or minimized by giving the injections in divided doses at different sites.

We are indebted to Professor F. R. G. Heaf for his help in arranging for our supplies of vaccine; to Dr. van Diense and Colonel Bensted for the freeze-dried vaccine ; to Professor Arvid Wallgren and Dr. J. H. Magnusson for generous gifts of B.C.G. tuberculin; and to our obstetric colleagues at St. Mary's Hospital for their willing co-operation.

REFERENCES

Debré, R., Brissaud, H. E., Mozziconacci, P., Cousin, Maud, and Kaplan, A. (1950). *Quart. Rev. Pediat.*, **5**, 143.
Heaf, F. R. G. (1950). *British Medical Journal*, **2**, 1353.
Magnusson, J. H., and Lithander, A. (1949). *Pediatrics*, **3**, 429.
Rekling, E. (1945). *Nord. Med.*, **27**, 1819.
Smith, H. V., and Vollum, R. L. (1950). *Lancet*, **2**, 275.
Ustvedt, H. J. (1951). *Conference of European B.C.G. Programmes*, p. 253. Heinemann, London.
Wallgren, A. (1950). *Tuberculosis and Other Problems of Pediatrics*, p. 33. Williams and Wilkins, Baltimore.

PETHIDINE AS AN ADJUVANT TO NITROUS OXIDE AND OXYGEN ANAESTHESIA

BY

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The scope of thiopentone in general anaesthesia, first popularized by Lundy in 1934, was enormously extended by the introduction of D-tubocurarine in 1942 by Griffith and Johnson. Administered by continuous intravenous drip or repeated fractional doses in combination with nitrous oxide and oxygen and, where indicated, a muscle relaxant, it has proved generally satisfactory in experienced hands.

This type of anaesthesia, however, is not without its disadvantages. Thiopentone is a powerful respiratory depressant with a weak analgesic action. Used with a gas-and-oxygen mixture, rich enough in oxygen to prevent anoxia, the amount required to obtund pain may cause undesirable respiratory depression, which, in long procedures requiring a relatively high total dose, may be prolonged into the post-operative period. Moreover, its powerful hypnotic but weak analgesic action is a cause of post-operative restlessness. The parasympathetic effect of thiopentone is, in theory at any rate, undesirable, especially when combined with a muscle relaxant, which, itself a potential liberator of histamine, may initiate bronchial constriction and spasm.

The search for a suitable adjuvant to nitrous oxide and oxygen anaesthesia led to the introduction into clinical anaesthesia of pethidine hydrochloride by Neff *et al.* (1947) in America, and by Mushin and Rendell-Baker (1949) in England.

First synthesized by Eisleb and Schaumann in 1939, pethidine is widely used in surgery and obstetrics for the relief of pain. Many other piperidine derivatives related to it have since been synthesized, and the properties of two of these—bemidone "10446" and keto-bemidone "10720"—have been described by Thompson and Neff (1950). They found the keto-compound "10720" to be fifteen to twenty times more powerful than pethidine, with which it compared favourably as an adjuvant to nitrous oxide and oxygen anaesthesia in dogs and human beings.

Unlike morphine, pethidine produces a high degree of analgesia without undue effect on the respirations and the blood pressure. It exerts a weak narcotic effect, thus allowing, in contradistinction to thiopentone, a rapid return to consciousness with delayed post-operative pain. It possesses, in addition, other properties, which have perhaps not been stressed enough by anaesthetists.

Professor J. H. Burn (1948) has drawn attention to the common action of a wide group of substances used medicinally. This group includes procaine, quinidine, atropine, the antihistamines, and pethidine. All have in greater or lesser degree a local anaesthetic action, the power to relax smooth muscle and to lengthen the refractory period of the heart, an analgesic and an antihistamine effect. Thus pethidine, in addition to its powerful analgesic action, has 80% of the activity of quinidine on the auricle, is similar in potency to procaine as a local anaesthetic, and has an antihistamine effect which is considerable. Burn (1950) suggested that intravenous pethidine would be more effective than procaine for the release of bronchial spasm in man. That it has a selective action on the laryngeal reflex has been shown by Ruben and Andreassen (1951), who, using intravenous pethidine alone, have intubated a series of 25 cases without eliciting laryngeal spasm.

The action of pethidine on the heart has been noted by Mushin and Rendell-Baker (1950), who, in over 100 thoracic operations, were particularly impressed by the absence of pulse irregularities when using gas and oxygen, gallamine triethiodide, and pethidine, and who suggest that this combination of drugs is especially suitable for operations on the heart.

Morphine is known to cause spasm of the lower end of the common bile duct near the sphincter of Oddi, yet it still continues to be used by anaesthetists and surgeons before and after operations on the biliary passages. Pethidine, because of its spasmolytic effect, is the drug of choice. Similarly, pethidine exerts a spasmolytic effect on the distal colon and rectum, and Griffiths (1950) has noted its value in combination with gas and oxygen in such operations as haemorrhoidectomy and posterior colporrhaphy.

The theoretical advantages of pethidine as a substitute for thiopentone in the maintenance of nitrous oxide and oxygen anaesthesia led me to try it in a large number of cases. In an attempt to arrive at a satisfactory standard technique use was made of wide variations in premedication, induction, and the dose and concentration of pethidine employed for maintenance. Premedication was with morphine and atropine, "omnopon" and scopolamine, pethidine and scopolamine, or pethidine and atropine in appropriate doses. In most cases thiopentone was used for induction, but some were induced with nitrous oxide and oxygen and others with cyclopropane. Intubation was performed under thiopentone and a muscle relaxant, thiopentone and cyclopropane, or a combination of all three. Maintenance was with nitrous oxide and oxygen, using a circle absorber or the semi-closed

method. The concentration of oxygen was kept at 30 to 50%. Pethidine was given in fractional doses varying between 20 and 50 mg. and in concentrations of 5 to 50 mg. per ml. The muscle relaxants used were gallamine triethiodide, D-tubocurarine, dimethyltubocurarine iodide, and decamethonium iodide.

Present Series

As a result of this preliminary trial a standard technique was evolved which was adopted in a series of more than 200 unselected cases. This series covers a variety of planned and emergency operations. Many were poor-risk cases of a high average age, the oldest patient being 98 and the youngest 12.

The results were uniformly good compared with other methods of anaesthesia. Notable features were the absence of respiratory depression, the relaxation of the bronchial tree, which greatly facilitated controlled or aided respiration, the rapid return to consciousness, and the prolonged post-operative analgesia. Fluctuations in the pulse rate and blood pressure were minimal. The high degree of analgesia was shown in patients allowed to come round too rapidly. When almost fully conscious they tolerated the endotracheal tube and seemed insensitive to skin suture.

This technique was found especially suitable when using hexamethonium bromide for controlled hypotension.

(i) Premedication

All patients in this series were given an intramuscular injection of pethidine and scopolamine one hour before operation, the dose for a healthy adult being 100 mg. of pethidine and 0.43 mg. of scopolamine. The sedation obtained appeared adequate and did not give rise to the respiratory depression which often occurs on the subsequent injection of pethidine in patients too heavily premedicated with morphine. This preliminary injection acted as a test dose and gave some indication of the subsequent pethidine requirements. It appeared to facilitate intubation and counteract the parasympathetic effect of thiopentone.

(ii) Induction

A 5% solution of thiopentone was used as a routine, but a 2.5% solution was found safer in old and shocked patients. The dose varied from 0.25 g. to 0.75 g. Intubation was performed under thiopentone and gallamine triethiodide.

(iii) Maintenance

This was with nitrous oxide through a circle absorber, using a concentration of 40–50% oxygen. Immediately normal respiratory rhythm was established pethidine was injected slowly, using 50 mg. in a concentration of 10 mg. per ml. for the average patient and 25 mg. in a concentration of 5 mg. per ml. in the old or debilitated. Subsequent doses, which varied between 20 and 50 mg., were given when indicated. Timing and dosage are a matter of experience, but 20 mg. every 20 minutes proved to be the average. Relaxation was maintained by gallamine triethiodide in 20-mg. doses when indicated.

A Gordh needle was found useful for the repeated injections, but it must remembered that when pethidine and thiopentone come in contact a milky precipitate is thrown down, due presumably to the marked difference in *p*H. The indwelling needle must therefore be cleared of all traces of thiopentone before pethidine is injected.

The total quantity of pethidine needed varied between 50 and 200 mg., but one patient, an extremely powerful young man, required 225 mg. during the course of an operation for reconstitution of the shoulder-joint. He was fully conscious within 20 minutes of the termination of the operation.

A more satisfactory procedure, especially in relatively long operations, is the administration of pethidine by continuous intravenous drip. By this method a more uniform level of anaesthesia is maintained and the total quantity of pethidine required has been found to be less than when administered in repeated fractional doses. A suitable dilution is 100 mg. of pethidine in 500 ml. of saline delivered from a graduated flask. The rate of flow is varied to suit the circumstances, but an average of 1 mg. of pethidine a minute has been found adequate to maintain satisfactory anaesthesia. The drip is progressively slowed down as the operation proceeds, being discontinued altogether before the end of the operation if a rapid return to consciousness is desired. Robust patients, however, may require an additional initial dose of 25 mg. (10 mg. per ml.). If a flask graduated in 100, 50, and 25 ml. is used the total dose of pethidine administered may be calculated at any time.

(iv) Post-operative Treatment

Pethidine has a weak narcotic effect. In the less painful procedures sleep can be procured on the night following the operation by a sedative such as one of the short-acting barbiturates. The more painful conditions require an analgesic post-operatively, but injection can usually be delayed until six or eight hours after recovery of consciousness. It is well to remind the nursing staff that pethidine is an analgesic and not a sedative.

Discussion

In the experimental series of cases pethidine was first given in a concentration of 50 mg. per ml. In a certain number of patients a single dose of 25 mg. caused pronounced respiratory depression, amounting in a few instances to complete apnoea for varying periods. In some cases a transient fall in blood pressure was noted. Since adopting a dilution of 10–5 mg. per ml. for intermittent injections and 0.2 mg. per ml. for continuous administration, no significant effect on the respirations has been observed.

D. Zuck (1951) reported prolonged apnoea and a profound fall in blood pressure in a patient given 25 mg. of pethidine following induction with thiopentone and gallamine triethiodide. It is worth noting that thiopentone, especially if administered rapidly, will cause an appreciable fall in blood pressure, and that pethidine potentiates the effect of the thiopentone. It is doubtful whether 25 mg. of pethidine, even if injected rapidly, in a concentration of 50 mg. per ml. would have such a profound effect on the circulatory and respiratory systems when given alone. It has been shown by Thompson and Neff (1950) that pethidine, given rapidly in doses of 5–10 mg. per kg. to anaesthetized dogs in a concentration of 50 mg. per ml., invariably produced a prompt and significant fall in blood pressure. When the injection was made slowly and the concentration reduced to 5–10 mg. per ml. no significant variation

of the blood pressure occurred. They found that slow injections of dilute solutions minimized the undesirable effects on respiration and circulation of piperidine derivatives resembling pethidine when administered to patients under nitrous oxide and oxygen anaesthesia.

Summary

The employment of pethidine hydrochloride as an adjuvant to nitrous oxide and oxygen anaesthesia has been discussed, with special reference to its anticholinergic and antihistaminic properties.

A method of maintenance by a continuous intravenous pethidine drip is outlined.

The importance of slow injections of dilute solutions is emphasized.

REFERENCES

Burn, J. H. (1948). *The Background of Therapeutics*. Oxford Medical Publ., London.
—— (1950). *British Medical Journal*, **2**, 691.
Griffiths, H. F. (1950). Ibid., **2**, 763.
Mushin, W. W., and Rendell-Baker, L. (1949). Ibid., **2**, 472.
—— —— (1950). *Brit. J. Anaesth.*, **22**, 235.
Neff, W. B., *et al.* (1947). *Calif. Med.*, **66**, 67.
Ruben, H., and Andreassen A. K. (1951). *Brit. J. Anaesth.*, **23**, 33.
Thompson, R. C., and Neff, W. B. (1950). *Curr. Res. Anesth.*, **29**, 77.
Zuck, D. (1951). *British Medical Journal*, **1**, 125.

POST-MORTEM EXAMINATIONS ON AIR-CRASH VICTIMS

BY

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On October 31, 1950, a Viking aircraft of British European Airways, flying from Paris to London, crashed in thick fog at London Airport. The wreckage burst into flames and 28 out of the 30 occupants of the plane were killed. Port-mortem examinations on all the victims were ordered by the coroner of the district, for the purposes of identification and to determine the cause of death. Since the religious tenets of many of the victims required a rapid burial the examination of the remains became something of an urgent problem.

Organization

The facilities of the local mortuary were not ideal for examination of such a large number of bodies. It had a refrigeration chamber for six, one fixed post-mortem table, and room for three trolleys. A marquee was set up close to the mortuary, in which the bodies were first placed and numbered. They were there stripped of such clothing as remained, and this was put into bags and similarly numbered. To assist in the identification, there were present a coroner's officer and a senior member of an undertaking firm, who had had experience in similar types of disaster. They had a complete passenger list of the occupants of the plane when it left Paris. There were two mortuary assistants and several bearers. The post-mortem reports were typed out directly in the mortuary by my secretary. The general principle employed was to examine those readily identifiable first, and so narrow down the number which might prove difficult of identification towards the end.

As it was thought necessary to estimate the carbon monoxide haemoglobin of each victim, 4 ml. screw-cap bottles were numbered in advance and 28 post-mortem reports were similarly numbered.

The specimens of blood were taken into these screw-capped bottles, filled to the brim to obviate any loss of carbon monoxide from the blood—a loss which may vitiate the value of a carboxyhaemoglobin estimation, particularly if the bottle is shaken in transport. Urea estimations were performed on the specimens of blood at varying intervals, up to seven days, in the hope of finding some variation which might assist in the estimation of the time of death in cases in which such time was unknown. They proved valueless.

Identification

Though most of the bodies were very severely burnt, particularly about the face and head, the problem of identification did not prove as difficult as was at first thought. Facial recognition was, except in a few cases, quite impossible, but in most cases the clothing of the chest and abdomen was relatively spared and passports were recovered from the inside coat pockets of the majority of the men. The women, keeping their passports in handbags, proved the more difficult to identify. The question of sex never presented any difficulty, but stature was difficult to estimate owing to the destruction and contortion of the limbs as the result of heat. The age could be roughly estimated by the state of the costal cartilages, skull sutures, and other skeletal changes.

As soon as a body was definitely identified, either by papers or by clothing, the name was added to the number on the body, on the clothing, and on the post-mortem report and specimen of blood. These steps led to the rapid identification of 25 of the victims. There remained two women and one man, and these three were all identified positively by means of their teeth. It must be remembered that, while a person's name may appear on the passenger list of a crashed aircraft, the relatives are not unnaturally loath to accept this as the only evidence of the death of one close to them. The man was an American, and his dental chart was transmitted from New York for identification.

The Cause of Death

The post-mortem examinations revealed several important points. All the victims had received injuries which would lead to immediate loss of consciousness or death. Twenty-three of the victims had no measurable concentration of carbon monoxide in their blood; three had less than 15%; and two between 15% and 20%. None of the latter showed any burning of the internal air passages such as is seen in the victims of a bursting boiler or the "flash and flame" discharge of a high-voltage electric current. It was reasonable to suppose, therefore, that most of the victims were dead before the outbreak of fire, and that the remainder, whose injuries were very severe, were unconscious and lived only for a matter of seconds in the fire. Furthermore, it would appear that had no fire occurred the fate of the occupants would have been the same. The actual causes of death may be summarized as follows:

Fractured skull	10
Fractured cervical spine	1
Traumatic subarachnoid haemorrhage	1
Ruptured aorta	8
Ruptured lungs	3
Ruptured heart	3
Ruptured liver and spleen	2

It will be seen that 16 of the 28 died of injuries to the chest and upper abdomen, and that, of these, eight had died of a most unusual injury—rupture of the aorta in its descending thoracic part. I have seen only three other cases of death from traumatic rupture of the aorta in 25,000 necropsies, and, of these three, one was the radio-operator of the Dakota which crashed at Mill Hill a fortnight earlier; the other two resulted from crushing injuries to the chest in traffic accidents. The radio-operator of the Viking was among those dying of rupture of the aorta.

The ruptures of the aorta were associated with fractures of the ribs, disruption of the intercostal muscles, fractures of the spine, or laceration and bruising of the anterior surface of the liver. These injuries were, in my opinion, caused by acute flexion of the body over the safety-belt. A similar mechanism could well have accounted for the findings in the eight who died from laceration of the heart, lungs, or liver and spleen. It would also appear that had these travellers been seated with their backs "to the engine" and supported by cushioned upholstery these particular types of injury might have been avoided.

It is clearly of little consolation to escape a sudden death only to die in a conflagration, but not all crashed aircraft catch fire, and presumably with advances in foam-protected petrol tanks the danger of fire will diminish.

Witnesses were not available to tell how the passengers in the aircraft were seated, but a study of the injuries revealed a remarkable similarity between the injuries of seven pairs of victims who might reasonably be expected to be sitting together. Thus two married couples all had ruptures of the aorta, another couple both had ruptures of the liver and spleen, while two men who had good reason to be seated together were the least severely injured—both sustained head injuries only, of a severity which suggested that had the speed of impact been a little less they might well have escaped. This is pure hypothesis, but suggests that certain parts of an aircraft are more dangerous than others in the event of a crash—a fact which is possibly obvious, and well supported by the escape of the steward of the Dakota at Mill Hill and the stewardess of the Viking, who were both in their correct positions in the tail of the aircraft.

Conclusions

Such a disaster as the crash of a passenger-carrying aircraft presents special problems to a pathologist called on to perform necropsies.

(1) The post-mortem examination of air-crash victims requires a small but efficient organization to facilitate identification and burial.

(2) Blood-urea estimations are of no value in estimating the time of death.

(3) The problem of identification should be approached by dealing with those easily identifiable first, and so narrowing the field of the more difficult cases.

(4) Identification by means of dental records is the most certain method in this class of accident.

(5) The immediate cause of death in more than half of the victims was acute flexion of the body over the safety-belt.

(6) This hazard might be lessened by air passengers travelling "back to the engine."

THE PROZONE PHENOMENON IN HAEMAGGLUTINATION REACTIONS

WITH SPECIAL REFERENCE TO THE QUANTITATIVE ANTIGLOBULIN TEST*

BY

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Quantitative studies of precipitin and flocculation reactions have shown that both require optimal proportions of antigen and antibody. It is well known, for instance, that a series of test-tubes in which decreasing amounts of diphtheria antitoxin are mixed with a constant amount of toxin often shows a "prozone" of antibody excess where the antigen-antibody complex remains soluble (Ramon, 1922). Similarly, a flocculating system of decreasing amounts of horse serum and a constant amount of rabbit antiserum shows a prozone where the antigen-antibody complex is soluble in an excess of antigen (Dean and Webb, 1926). Many other examples have been published since these original reports.

It is well known, of course, that the optimal ratio differs for each antigen-antibody complex if either the constant antigen or the constant antibody technique is alternately used. But this has no bearing on the fact that prozones are in both cases due to an excess of antigen or antibody where the complex is "protected" against the precipitating effect of environmental factors, especially of salts.

Prozones have also been met with in the agglutination reactions. In this particular case of the antigen-antibody reaction, however, it is noteworthy that each bacterial or red cell has a fixed "load" of antigen. As the agglutination can be easily read only in a very narrow range of strength in the cell suspension, it is very difficult to vary the antigen concentration in the system. The prozones observed in agglutination reactions are then always situated in the antibody-excess range and could be interpreted as a purely quantitative phenomenon.

Other explanations have arisen from the study of these prozones. Shibley (1929), for instance, observed prozones with moderately heated agglutinating antisera, and postulated that heat had modified the agglutinin into an agglutinoid which combined with the antigen without bringing an agglutination. He showed, indeed, that the cells within the prozone were subsequently unagglutinated by an agglutinating dose of fresh antiserum. The work by Bawden and Kleczkowski (1942) suggests that heat would combine some serum albumin with the antibody molecules and induce the blocking property.

On the other hand, with the discovery of the blocking effect in anti-Rh sera, Wiener (1944) suggested that blocking antibodies could be held responsible for the prozone phenomena met with in titrations of anti-Rh sera. This interpretation was supported by a blocking effect within the prozone.

While studying prozone-giving anti-Rh sera Levine and Waller (1946) observed that suitable absorption

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removed the blocking antibody, thus suppressing the prozone without any appreciable effect on the final titre of the agglutination.

Present Investigations

In various experiments in which blood from different species was injected into rabbits we have seen that after an inversion of the optimal temperature for activity (Millet and Hubinont, 1946) there is a further change in the agglutination pattern—namely, the development of a prozone (Hubinont, 1948) which gives a blocking effect—thus substantiating the opinion that it is due to the presence of blocking antibodies. It is noteworthy that these experimental prozones were found as the result of prolonged immunization, and also that they appeared quite regularly after a time, varying probably with the antigenic strength of the material injected and the individual response of the rabbit.

Quite similarly we found that the preparation of rabbits by injecting human globulins—alum-precipitated, following Proom (1943)—could lead to a definite prozone phenomenon when the anti-human-globulin serum so obtained was titrated with sensitized Rh-positive cells. In a certain number of cases we observed that the indirect Coombs test was positive in a very small range of dilutions of the anti-human-globulin serum, and we recommended that several dilutions of the reagent should be used before deciding that there was no sensitization (Hubinont and Massart-Guiot, 1950). Further, we were able to show that the prozone given by these particular anti-human-globulin sera was inversely proportional to the titre in albumin of the sensitizing anti-Rh serum. Thus we concluded that the range of the prozone was dependent on the degree of sensitization of the cells (Table I).

TABLE I.—*Sensitization of CDe/cDE cells by anti-D Sera of Increasing Potency (as Judged by the Titre in Albumin) (Hubinont and Massart-Guiot, 1950)*

Name of Anti-D Sera	Titre in Albumin with CDe/cDE Cells	Increasing Dilutions of the Anti-globulin Serum (PR_4b)								
		1/2	1/5	1/10	1/20	1/50	1/100	1/200	1/500	1/1000
Dew	2^{-4}	−	±	−	−	−	−	−	−	−
Mer	2^{-3}	−	−	−	±	−	−	±	+	++
For.	2^{-5}	−	−	−	?	+	+	++	++++	++++
Laur.	2^{-7}	−	±	++	+++	++++	++++	++++	+++	++++
Berg.	2^{-7}	+	++	+++	+++	++++	++	++	++++	++++
Beekm.	2^{-8}	+	++	+++	++++	++++	++++	++++	++++	++++
Fr.	2^{-14}	++	++	+++	++++	++++	++++	++++	++++	++++
Free.	2^{-18}	++	+++	++++	++++	++++	++++	++++	++++	++++

Independently, Van Loghem *et al.* (1950) had studied similar anti-human-globulin sera and, by sensitizing Rh-positive red cells with serial dilutions of anti-Rh sera, showed that the prozone phenomenon increased when the preliminary sensitization decreased. In explaining the phenomenon, they postulated (extending Wiener's views on prozones in agglutination by anti-Rh sera) that the antiglobulin serum should contain blocking antibodies (univalent) together with agglutinating antibodies (bivalent) at a higher titre, the former being responsible for the prozone when weakly sensitized cells are used.

Coombs (1950, personal communication) suggested that an excess of bivalent antibody by itself could interfere with the "lattice" formation, and eventually the addition of suitable amounts of gamma globulin (human) induced the agglutination within the prozone (see Van Loghem *et al.*, 1950).

Thus the meaning of the prozone remains open to discussion. Either it is due to an excess of a unique antibody or it results from a blocking effect by a blocking antibody which should then coexist with an agglutinating antibody.

We have thought that the anti-human-globulin reaction could shed some light on the problem, for, unlike the haemagglutination reactions ordinarily met with, the amount of antigen could be varied in a very large range and, consequently, quantitative aspects of the antigen-antibody reaction could be studied also with the constant antibody technique. We have therefore carried out investigations with prozone-giving anti-human-globulin sera in the following way.

Experiment I

An equal quantity of O M CDe/cDE 1/5 suspension in saline was mixed in tubes with 128 volumes of two-fold dilutions in AB human serum of a strong blocking anti-D serum (titre 2^{-14} when 30% bovine albumin (Armour) was used as diluent). The tubes were incubated at 37° C. for two hours. The cells were washed six times in physiological saline, and quantitative anti-globulin tests were performed on slides, the readings being recorded after ten minutes' gentle rocking.

We used AB serum as a diluent for the first stage (sensitization) in order to get a uniform sedimentation rate of the red cells, uniform environmental conditions, and also the same protein concentration when starting the washing. It was therefore believed that the chances that the antigen-antibody reaction would occur would be the same in all tubes, and, on the other hand, that there would be, if any, an equal aspecific absorption of the antiglobulin antibody by residual serum proteins after washing the cells in saline.

The result of this experiment is given in Table II. This can be read horizontally and vertically, giving the agglutination pattern either with constant antigen or with constant antibody titrations. It appears that both an excess of antigen and an excess of antibody correspond to a prozone where anti-human-globulin serum agglutinated sensitized Rh-positive cells, the result of the above-mentioned experiment being similar to observations in flocculation reactions.

The prozone met with in the constant antigen readings gave, of course, a blocking effect when an agglutinating dose of anti-human-globulin serum was added to the unagglutinated cells.

As there was a considerably lower titre of the anti-human-globulin serum when titrated with very strongly sensitized cells, we wondered if the very strong sensitization could not have brought down with the cells a greater quantity of aspecific serum proteins of which

TABLE II.—*Optimal Ratio Between the Degree of Sensitization of Rh-positive Cells and the Dilutions of Anti-human-globulin Serum*

Degree of Sensitization of CDe/cDE Cells (Washed) 6 Times	Increasing Dilutions of Anti-globulin Serum (PR_1b)										Saline
	1/1	1/5	1/10	1/50	1/100	1/500	1/1000	1/5000	1/10,000	1/50,000	
128/1 ..	+++	++	±	−	−	−	−	−	−	−	−
64/1 ..	++++	+++	++	+	−	−	−	−	−	−	−
32/1 ..	++++	++++	+++	++	+	?	−	−	−	−	−
16/1 ..	++	+++	++++	+++	++	++	±	−	−	−	−
8/1 ..	±	++	+++	+++	+++	+++	++	+	±	−	−
4/1 ..	?	++	++	++++	++++	++++	+++	++++	+	?	−
2/1 ..	−	±	+	+++	++++	++++	++++	+++	+++	+	−
1/1 ..	−	±	+	+++	++++	++++	++++	++++	+++	+	−
1/2 ..	−	−	±	++	++++	++++	++++	++++	+++	?	−
1/4 ..	−	−	±	++	+++	+++	++++	+++	++	±	−
1/8 ..	−	−	?	+	++	++	+++	+++	++	?	−
1/16 ..	−	−	−	±	++	++	+++	++	±	−	−
1/32 ..	−	−	−	−	?	±	++	+	−	−	−
1/64 ..	−	−	−	−	−	−	+	±	−	−	−
1/128 ..	−	−	−	−	−	−	±	±	−	−	−
Unsensitized cells ..	−	−	−	−	−	−	−	−	−	−	−

the washings did not remove all traces in spite of the precautions described above. This was, however, very improbable, owing to the fact that supernatants gave a very slight but identical precipitate when tested with trichloracetic acid after the fifth washing.

In order to avoid this bias up to a certain point we made the following experiment.

Experiment II

O M CDe/cDE packed cells were sensitized with a very powerful anti-D serum (titre 2^{-18} in 30% bovine albumin). After incubation for two hours at 37° C. they were washed six times in physiological saline. In another test-tube the same cells were mixed with equal proportions of human AB serum, incubated and washed in the same way as the sensitized cells. Sensitized and unsensitized cells were then mixed in various proportions in order to obtain identical volumes of suspensions of the same strength. These tubes were thoroughly shaken in order to ensure an even distribution of sensitized and unsensitized cells, and incubated for an extra hour. Quantitative antiglobulin tests were performed after resuspending the sediment in its own supernatant.

Table III shows that by mixing sensitized with unsensitized cells it is possible to reproduce a quantitative agglutination pattern which is quite similar to the one obtained in experiment I. When fresh cells are added to sensitized cells there is a remarkable decrease of the sensitization, for which a dilution effect cannot account, because (for instance in the 1/9 mixture) 1/100 and 1/500 dilutions of the antiglobulin serum gave a ++ reaction when most of the cells were involved. Examination under a low-power microscope showed that more than 90% of the cells were agglutinated, while in the original mixture only 10% were sensitized by the anti-D serum.

Thus when mixing fresh to sensitized cells there seems to be a redistribution of the antibody amongst the cells, with the final result of a lessened statistical sensitization.

Arguments for a labile binding between the cell antigen and the Rh antibody could also be based on experiments, to be reported elsewhere, in which we were able, by washing, to " desensitize " Rh-positive sensitized cells up to a point where the antiglobulin reaction became negative, though the agglutinability of the cells was retained.

It should be remembered that Morgenroth produced a similar phenomenon by adding unsensitized to sensitized rabbit cells, all the cells undergoing haemolysis when complement was subsequently added.

Conclusion

Our data strongly suggest that the prozone phenomenon (at least in certain haemagglutination reactions) is more satisfactorily explained by a purely quantitative reaction between antigen and antibody in the antibody-excess ratio, when the constant antigen titration is used.

It is not claimed that there is absolute evidence that the prozone is not due to the presence of blocking antibody in the anti-human-globulin serum. But if we consider that the constant antibody technique gives also a prozone where the action of a " blocking antigen " is excluded up to a high probability, and that the reactions between sensitized cells and the dilutions of the anti-human-globulin serum suggest a linear relationship in the optimal proportions of antigen and antibody, the close analogy of the prozone phenomenon to precipitin or flocculation reactions is against any qualitative kind of explanation.

It would be of great interest to generalize our observations to other antigen-antibody reactions by varying the

TABLE III.—*Effect of Adding Fresh Cells in Various Proportions to Sensitized Cells*

Proportion between Sensitized Fresh Cells	Increasing Dilutions of Anti-globulin Serum (PR_1b)										Saline
	1/1	1/5	1/10	1/50	1/100	1/500	1/1000	1/5000	1/10,000	1/50,000	
10/0 ..	±	+	++	++++	++++	++++	+++	−	−	−	−
9/1 ..	−	±	++	++++	++++	++++	++++	±	−	−	−
7/3 ..	−	?	+	+++	++++	++++	++++	+++	++	+	−
4/6 ..	−	−	±	++	+++	+++	++	++	+	?	−
1/9 ..	−	−	−	+	++	++	+	±	−	−	−
0/10 ..	−	−	−	−	−	−	−	−	−	−	−

amount of antigen on the cell's surface, or by the collodion-particle technique where this prospect could be more easily realized. We have carried out such an experiment with the agglutinating system "blocking" anti-D-trypsinized cells. A preliminary note on this subject will be published (Hubinont, 1951).

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REFERENCES

Bawden, F. C., and Kleczkowski, A. (1942). *Brit. J. exp. Path.*, **23**, 169.
Dean, H. R., and Webb, R. A. (1926). *J. Path. Bact.*, **29**, 473.
Hubinont, P. O. (1948). *C.R. Soc. Biol., Paris*, **142**, 1458.
—— (1951). *Nature, Lond.* (to be published).
—— and Massart-Guiot, T. (1950). *Rev. Hémat.*, **5**, 340.
Levine, P., and Walker, R. K. (1946). *Science*, **103**, 389.
Millet, M., and Hubinont, P. O. (1946). *C.R. Soc. Biol., Paris*, **140**, 1227.
Proom, H. (1943). *J. Path. Bact.*, **55**, 149.
Ramon, G. (1922). *C.R. Soc. Biol., Paris*, **86**, 661.
Shibley, G. S. (1929). *J. exp. Med.*, **50**, 825.
Van Loghem, J. J., *et al.* (1950). *Maandschr. Kindergeneesk.*, **18**, 115.
Wiener, A. S. (1944). *Proc. Soc. exp. Biol., N.Y.*, **56**, 173.

THE INJECTION TREATMENT OF HYDROCELES AND SPERMATOCELES

BY

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Despite the antiquity of injection treatment of hydroceles and spermatoceles there is still no general agreement regarding its value. The diversity of injection material is perhaps an indication that none is entirely successful, reflecting the multitude of operating techniques. The surgeon who promises a patient a brief stay in hospital, early return to work, and freedom from recurrence has either a short memory or little experience. It is felt that, if injection therapy has anything to offer, there is a place for it in the treatment of hydroceles and spermatoceles. It has been used sporadically in this hospital over a number of years, but unfortunately the records do not permit investigation of out-patients treated before 1948, when a new system of documentation was introduced. A fresh wave of enthusiasm for injection began in March, 1948, and it is the effect of this wave that I have attempted to discover.

Cases

The distribution of the cases is shown in Table I. The hydrocele clinic was a special clinic held on Saturday mornings for the repeated aspiration of hydroceles and spermatoceles. One patient had been attending for 40 years, several for more than 10 years; the average was about 5 years. The cases have been divided into frequent (average interval of three to four months between aspirations) and infrequent attenders (interval greater than a year). Each patient who attended the hydrocele clinic was injected at his first visit after March, 1948. Patients attending the hospital for the first time were seen by either a consultant surgeon or the R.S.O. acting as his deputy. All patients seen by the R.S.O. were referred to the hydrocele clinic for trial of injection before consideration of operative treatment. Of the patients seen by consultants, some were advised operation, some were reassured that no treatment was necessary, and others were referred to the hydrocele clinic: a few were treated by immediate aspiration (see Table I). To this extent the material is selected, probably accounting for the small proportion of young patients in the series. Many of these patients had been treated by their own doctors for some time, being referred to hospital either because of the increased pressure of work with the advent of the National Health Service or because they expressed a wish for operative treatment, being tired of repeated aspiration.

TABLE I.—*Number of Lesions*

		Total No.	Operation Advised	No Treatment	Aspiration	Aspiration + Injection
Hydrocele clinic		66	1	—	5	60
New patients:						
1948	Hydrocele	61	23	4	2	32
	Spermatocele	29	12	2	1	14
1949	Hydrocele	53	21	1	8	23
	Spermatocele	28	9	2	1	16

Eight patients had bilateral lesions. Many of the patients for whom operation was suggested had an associated lesion (e.g., hernia) for which operation was advisable.

The distinction between a hydrocele and a spermatocele, while usually simple, is not always made, and in several cases it has been difficult to decide from the documents whether "hydrocele" meant in fact a hydrocele of the tunica vaginalis, or whether it was being used as a generic term for a fluid swelling in the scrotum. When the fluid has been aspirated several times it is often very difficult to be sure of the diagnosis; no attempt has therefore been made to classify the hydrocele cases attending the clinic as old patients.

Technique

A few patients were injected with "ethamolin"; this treatment was stopped when it was discovered that severe pain occurred, followed by collapse, the patient becoming cold, with a thready pulse. All cases recovered after resting for a few hours. I have not seen this collapse after injecting ethamolin into varicose veins, and do not think the reaction can be anaphylactic in nature. In one case procaine was injected after emptying the sac, five minutes before the ethamolin; the patient did not complain of pain and showed no untoward reaction—this supports the suggestion that the collapse is neurogenic—but he collapsed in the tram on his way home, and was confined to bed for two weeks with a red, painful, swollen scrotum, which subsided without discharge. This treatment seemed to be too drastic, and was abandoned, although the patient, who had been attending for aspiration of a spermatocele every two months, stated at a review two years later that "it was worth it," for there had been no return of fluid. It has not been possible to trace the records of the other patients who were treated in 1947; they have not attended hospital since, and so have not been included in the present series.

Quinine-urethane has been used since March, 1948. It has been prepared in the hospital dispensary, the following being the prescription:

Quinine hydrochloride	4 g.
Urethane	2 g.
Distilled water	to 30 ml.

The hydrocele sac is emptied as completely as possible, using a trocar and cannula, and 4 ml. of quinine-urethane is injected through the cannula. For a small spermatocele

a large-bore needle and syringe is easier to use. A multilocular collection of fluid presents difficulty; usually the whole injection was given into the largest loculus, but sometimes it was divided between two large loculi. Pain is unusual, and many patients were unaware that an injection had been given. At first each patient was asked to attend again after a fortnight. Almost invariably there had been rapid reaccumulation of fluid: in some cases this was simply aspirated; in others a second injection was given. Later, patients were just asked to return as usual—"when the fluid comes back"—and were injected again on their return; this is the technique that we favour at present. After the injection there is a rapid effusion into the sac; in a favourable case this reaches a maximum after about two weeks, then is gradually absorbed in the course of about two months.

Most cases were treated by students under supervision, and some by house-surgeons unfamiliar with the exact technique; this accounts for a certain variation in the details of treatment. A technical point worthy of note is that in the cold the quinine tends to crystallize from the solution. These crystals, which are easily seen if the bottle is examined, dissolve readily on warming. If attention is not paid to this detail the concentration of quinine in the injection may be low.

Review

Most of the patients were seen personally during April and May, 1950. It is surprising how large a collection of fluid may pass unnoticed by a patient who has had a hydrocele for years; many of those who were classified as only improved, and some of the failures, expressed the opinion that they had been completely cured by the treatment. In only a few cases, therefore, was a letter from the patient regarded as sufficient. Five of the patients died, and one spermatocele was excised during operation for an inguinal hernia before the effect of the injection could be seen. In two cases it was felt to be too early to make even a guess at the effect of the injection. Most of the remaining missing patients had changed their address and could not be traced. It is thought that the 128 lesions reviewed represent a fair sample of the whole; they have not been subject to selection in any way.

Results

The results are shown in Table II. The effect of treatment was considered to be satisfactory if there was a complete absence of fluid, or less than 2 oz. (57 ml.) without any suggestion of a gradual increase. In many cases there was a very small amount of fluid which could be manipulated into any part of the tunica vaginalis; this is not in keeping with the theory that obliteration of the tunica vaginalis is produced by injection therapy.

TABLE II.—*Results of Treatment*

	Total No.	No. Reviewed	Satisfactory	Improved	Failure
Hydrocele clinic:					
Frequent tapping ..	46	41	31	9	1
Infrequent tapping ..	14	13	5	5	3
1948 Hydrocele ..	32	26	16	4	6
1948 Spermatocele ..	14	11	6	4	1
1949 Hydrocele ..	23	22	15	2	5
1949 Spermatocele ..	16	15	9	2	4
	145	128	82	26	20

The numbers refer to lesions, not patients. The results on the two sides were not always the same.

In others there was a small amount of fluid at the upper pole of the testis. Whether this represented a localized collection of fluid in the tunica vaginalis or a true spermatocele is difficult to say, but the presence of a similar swelling on the opposite side in many cases suggested that the latter explanation was the correct one. After injection of a spermatocele it was common to find a firm nodule the size of a pea in the epididymis. An improvement was considered to have taken place if the interval between aspirations was appreciably lengthened or if the hydrocele content was much smaller than before treatment and was not increasing.

Before this review was undertaken it was known that some cases had derived great benefit and that others must be classified as failures. It was hoped that a survey of the series might provide some basis for predicting the effect of injection therapy. However, analysis of the cases by age, size of hydrocele, length of history, and detailed technique of treatment does not reveal any marked difference in results. On the whole, cases requiring frequent aspiration responded better than those whose fluid accumulated only slowly, but there were many exceptions to this. I believe that the method is worthy of trial in any type of case.

Complications

Pain severe enough to be recorded or remembered occurred in nine cases. One patient was off work for three days, another for one day. The remainder did not stay away from work, but it must be remembered that most of the injections were given on Saturdays.

Inflammation.—In another case pain after injection was accompanied by redness and swelling of the scrotum, with a pyrexia of 102° F. (38.9° C.), confining the patient to bed for two days. The reaction settled without discharge and there has been no return of fluid. While this reaction may have been a chemical inflammation in a patient with an idiosyncrasy to the material injected, bacterial contamination was perhaps more likely.

Haemorrhage.—In several hydroceles tapped two weeks after injection the fluid was brown, owing to the presence of altered blood. In two cases bleeding was sufficient to produce a clotted haematocele, resistant to aspiration: one of these cases became infected and was drained two months after injection; the other refused operative treatment, and the haematocele was unchanged at review fourteen months later. Haemorrhage is not an uncommon complication of tapping alone, and it is not certain that the injection can be held to blame for this incident. During 1948 two patients were admitted to this hospital as emergencies, with haematoceles following aspiration by their own doctors.

Illustrative Cases

Case 1.—Aged 72. Attended the hydrocele clinic for 40 years, having 15 oz. (425 ml.) of fluid aspirated every three months. On April 10, 1948, 4 ml. of quinine-urethane was injected. On April 24 7 oz. (200 ml.) of fluid was aspirated and a further injection of 4 ml. given. At a review on April 19, 1950, there was no fluid in the scrotum.

Case 2.—Aged 78. Attended the hydrocele clinic for 16 years, having 10 oz. (284 ml.) of fluid aspirated every six months. A single injection of quinine-urethane was given on April 17, 1948. At a review on April 19, 1950, there was a small hydrocele containing about 2 oz. (57 ml.) of fluid.

Case 3.—Aged 61. Attended the hydrocele clinic for four years, having 10–16 oz. (284–454 ml.) of fluid aspirated every two to three months. The first injection of quinine-urethane was given on June 12, 1948. On December 4, 1948, 13 oz. (368 ml.) of fluid was aspirated and injection repeated. At review on April 12, 1950, there was no fluid in the scrotum.

Case 4.—Aged 69. Attended the hydrocele clinic for 18 years, having 10 oz. of fluid aspirated every four months. Injected on April 3, 1948. There was a sudden recurrence of fluid during February, 1950; injection was repeated. This case is classified as "improved."

Case 5.—Aged 62. First attended with hydrocele on April 3, 1948, when 30 oz. (850 ml.) of fluid was removed and 4 ml. of quinine-urethane injected. On May 3, 1950, he had a spermatocele containing about 1 oz. (28 ml.) of fluid.

Case 6.—Aged 57. Attended with a spermatocele from which his own doctor had removed 2 pints (1.14 litres) of fluid in September, 1947. On March 19, 1948, 2 pints of clear fluid was withdrawn, and 15 ml. of quinine-urethane injected by a house-surgeon; the patient remembers no reaction. On June 21, 1950, he had bilateral small spermatoceles, none bigger than a pea.

Case 7.—Aged 42. Hydrocele for one year; no previous treatment. On January 31, 1949, 60 oz. (1.7 litres) of fluid was removed and 4 ml. of quinine-urethane injected; on February 12, 13 oz. was removed and injection repeated; on February 26, 10 oz. was removed and injection repeated; and on March 12, 4 oz. of fluid was removed. On May 24, 1950, there was no fluid in the scrotum, but some thickening of epididymis.

The cases under review include three "hydroceles" which recurred after operation. It was also revealed that six patients had had previous injections: one as early as 1930, when 1.5 ml. of quinine-urethane was injected without improvement; another in 1933, when 2 ml. of quinine-urethane produced no effect; neither of these patients attended again after two injections of quinine-urethane in 1948, and unfortunately they are not available for review, one having died and the other having left the area. Another patient, injected in 1940 (injection fluid not specified), remained free from fluid until 1948; this illustrates the difficulty in determining the value of injection treatment, but perhaps few patients would undergo operative treatment to avoid injections every eight years.

Discussion

Review of the literature is rather disappointing. Many patients with hydroceles are old and have a short expectation of life, and not all hydroceles refill rapidly after simple tapping. It is expected, therefore, that, as in this series, a certain number of the patients in an unselected series will die before the effect of the injection can be judged, and any series that claims 100% cure may be regarded with suspicion. James (1941), reporting a case of "giant" hydrocele—64 oz. (1.8 kg.)—treated by injection of "lithocaine" followed by quinine-urethane, mentioned that he had had complete success in every one of his series of 74 cases. Diamond (1942) claims the cure of 76 cases, using a single twin injection of lithocaine and quinine-urethane, the patient remaining in bed for two to three days until comfortable. Cases coming to necropsy four to five years after injection showed complete obliteration of the tunica vaginalis by soft elastic fibrous tissue. He admits no failures, but does not mention the length of observation. Foote (1945) recommends the injection of procaine before quinine-urethane and lithocaine to prevent pain, not mentioned by James; he advises quinine-urethane for routine use, lithocaine being employed for failures or recurrences, but does not give any results. Ewell *et al.* (1940) and Bruskewitz and Ewell (1948) advocate the use of quinine-urethane, 1–2 ml. weekly for three injections, repeated later if necessary; one patient received 17 injections. They had seven failures or recurrences in 165 cases, but it is disturbing to read that one patient was operated on a month after "cure" by these injections—surely a premature assessment of the result.

When injection treatment was reintroduced at the hydrocele clinic, one of the prime considerations was that it should entail little inconvenience to the patients, most of whom were old. Many of them accepted as a condition of old age the fact that they had to attend every three months for tapping, and it was interesting to see what improvement could be produced without increasing the burden of treatment to which they were resigned. As stated above, many did not notice any departure from the normal routine of tapping, and were surprised that the fluid did not return. The period of observation is short; some of the "satisfactory" cases may disappoint by recurrence; and perhaps more of the failures may show response to later injections. It would be interesting to know how many would respond to other types of injection; but, despite the opinion of the patient treated with ethamolin preceded by procaine, it is thought that most patients would rather attend regularly for tapping than spend a few days in bed with a painful scrotum.

Summary

Most of the 145 hydroceles and spermatoceles treated by the injection of quinine-urethane since March, 1948, received only one injection. Pain was reported in less than 10%, and other complications were rare.

Of 128 lesions reviewed, 82 were considered satisfactory in that they were either free from fluid or contained a small quantity which could be detected only by careful examination. Twenty cases were assessed as failures.

Cases requiring frequent tapping responded better than those whose fluid accumulated only slowly.

Review of the literature suggests that better results may be obtained by the additional injection of lithocaine, but it is doubtful whether the increased disturbance justifies its use in the majority of patients.

My thanks are due to all the consultant surgeons of the General Infirmary at Leeds for permission to treat and review their cases, and to many students and house-surgeons, notably Mr. J. F. Scarlett and Miss Diana Elkington, for assistance.

References

Bruskewitz, H., and Ewell, H. (1948). *J. Urol.*, **59**, 67.
Diamond, J. C. (1942). *Amer. J. Surg.*, **55**, 121.
Ewell, G. H., *et al.* (1940). *J. Urol.*, **44**, 741.
Foote, R. R. (1945). *Postgrad. med. J.*, **21**, 133.
James, W. L. (1941). *British Medical Journal*, **2**, 693.

A medical teaching mission, composed of 14 specialists from six different countries, is now visiting Israel. Clinical and other specialists of the mission will spend one month in Israel, after which they will go to Persia for three weeks. The public health unit of the mission, directed by Dr. Karl Evang, of Norway, a former president of the World Health Assembly, will remain in Israel for two months. Mission members will work with specialists in their own fields, give lectures and demonstrations, visit hospitals and medical schools, exchange information, and attend conferences.

ACUTE SUBDURAL HAEMATOMA IN INFANCY AND CHILDHOOD

BY

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Although the clinical pictures of the various types of subdural haematoma merge into one another, it is helpful to consider separately an acute variety unassociated with intrinsic cerebral injury, because in children it presents an urgent problem requiring prompt diagnosis and treatment if fatalities are to be avoided. The peak incidence is in early life, at a time when, as Ingraham and Matson (1944) have pointed out, the significance of trauma is most difficult to assess. In this paper we shall consider rapid compression of the brain by surface clots as a paediatric emergency. The following case is an example of the condition and is reported because it raises a diagnostic difficulty which has received but scant attention.

Case Report

The patient, a 13-month-old girl, was admitted to hospital on December 9, 1949. She was one of a pair of binovular twins. Her mother had been treated for anaemia, hyperemesis, and hydramnios during the pregnancy, but the child was delivered normally at term and caused no anxiety. Head moulding was not excessive. She was bottle-fed from birth and given orange juice and cod-liver oil daily. Her progress was normal; at the time of admission to hospital she weighed 21 lb. (9.5 kg.) and all the incisors were present. According to her mother she had always been pale and had bruised easily. There had been no spontaneous haemorrhages. In addition to her twin sister there are two other children, and all are healthy. Her father has suffered from urticaria and her mother from anaemia, which has responded to iron treatment. There is no consanguinity.

At 4.45 p.m. on December 9 the child, who was sitting playing on the floor, suddenly heeled over and had clonic convulsions involving the right arm and leg. After a few minutes she became limp and stuporous. When seen at 5.30 p.m. she was still in this condition. A bruise on the right cheek and one on each leg contrasted with her general pallor. The left lid was closed and the pupil was dilated but reacted to light. All limbs were completely flaccid and there was no neck rigidity. A history of injury could not be obtained, though minor bumps and tumbles could not be excluded.

By the time she was admitted to hospital three-quarters of an hour later the picture had changed in certain particulars. There was no ptosis and the pupils were equal; the eyes were deviated to the left. The right arm was flaccid and externally rotated; the other limbs moved normally. The right biceps-jerk was absent, the right knee- and ankle-jerks were exaggerated, and the right plantar response was extensor; the abdominal reflexes were absent; the fundi were normal; the head was not enlarged; and the anterior fontanelle was closed. The pulse was irregular, the rate being 80. Respirations were sighing, and she yawned frequently. She was still in a stuporous state but could be made to swallow fluids. Lumbar puncture was performed and 3.5 ml. of clear colourless fluid was withdrawn. It contained protein, 40 mg. per 100 ml.; chlorides, 620 mg. per 100 ml.; and 2 cells per c.mm. Culture was sterile. A blood count showed: red cells, 2,700,000 per c.mm.; Hb, 44%; platelets, 102,000 per c.mm.; white cells, 20,000 per c.mm. (neutrophils 70%, lymphocytes 26%, monocytes 4%). A blood culture was sterile.

By next morning her colour was better and she was easier to feed, but there was still no spontaneous activity and the neurological signs were unchanged. The improvement was not maintained and by evening she had become ashen grey and semicomatose. The pulse had slowly risen during the day to 120 and the temperature to 102° F. (38.9° C.). At a second lumbar puncture the pressure was 180 mm. and the fluid was clear and colourless.

On December 11 two small flame-shaped haemorrhages were seen in the temporal half of the right fundus, one above and one below the disk. There was ptosis of the left lid; both pupils were dilated, but reacted briskly to light. The eyes still deviated to the left. There was now a right flaccid hemiparesis. The right plantar response was still extensor. The temperature had risen to 103.8° F. (39.9° C.) and the pulse to 130. Coma deepened and the child could be fed only with a stomach tube. At 9 p.m. clonic convulsions involving the right arm and leg occurred and lasted several minutes. The child died at 1 a.m. on December 12 after a further convulsion.

Pathological Findings.—At necropsy the body was that of a pale well-nourished child. A large, recently clotted subdural haemorrhage was found on the left side, extending from the posterior part of the frontal lobe backwards and downwards over the temporal and occipital lobes. There was no evidence of membrane formation. On a parietal branch of the left middle cerebral artery a small tag was seen. When this was teased out under water and examined with a hand lens no aneurysm could be made out and no tear was seen. Its significance remains obscure. The brain was normal and no fracture of the skull was found. The other organs were normal macroscopically. On microscopy the spleen and liver were normal and there was no evidence of extramedullary haemopoiesis.

Comment

The clinical picture was one of a rapidly progressive intracranial lesion with localizing signs. Subarachnoid haemorrhage and meningitis were excluded on the C.S.F. findings. The impairment of consciousness, combined with right-sided hemiplegia and incomplete left third nerve palsy, was taken to indicate the development of a tentorial herniation due to increasing intracranial haemorrhage rather than an inflammatory or thrombotic process. Diagnosis of a surface clot, as opposed to cerebral haemorrhage, was rendered difficult by the absence of a history of injury and by the acuteness of the illness; their differentiation is discussed below. No cause, such as scurvy or purpura haemorrhagica, could be found to account for the anaemia and the tendency to bleed, nor was the source of subdural bleeding discovered at post-mortem examination.

Discussion

This case illustrates the need to consider a rapidly forming subdural haematoma as an alternative diagnosis to spontaneous cerebral haemorrhage in the young, who are so liable to unwitnessed and unheeded injuries. When the clinical pictures are compared it is surprising that their differentiation is so seldom discussed. Both have an acute onset with disturbance of consciousness and share the secondary effects of intracranial bleeding, such as fever, leucocytosis, and retinal haemorrhages. Localizing signs are expected in cerebral apoplexy and are also common with subdural bleeding. Neither the progression of the focal or general signs nor the presence

of a unilateral dilatation of the pupil can always be relied upon to distinguish between the two lesions. The findings on lumbar puncture may be more helpful. Few red cells should be present in the cerebrospinal fluid in acute subdural haematoma without brain laceration, in contrast to the grossly bloody fluid found by Aring and Merritt (1935) in over 70% of cases of cerebral haemorrhage. The special methods of investigation are disappointing once puncture of the subdural space becomes impossible owing to fusion of the cranial sutures. Storch and Munro (1938) found encephalography of little use in all but large chronic subdural haematomata. Angiography is capable of yielding valuable information, but is technically difficult in a gravely ill child and is likely to lead to dangerous delay in operating.

The practical importance of this problem is brought out by Sheldon's (1927) analysis of 10,150 consecutive post-mortem examinations at the Hospital for Sick Children, Great Ormond Street. He found 50 cases of intracranial haemorrhage in children under 12 years of age, of these, only eight were attributed to trauma. The number of cases in the first year of life was much greater than in subsequent years even if those due to labour are excluded. He found that, in contrast to the commonness of intracerebral haemorrhages in adults, in his series the majority of haemorrhages occurred outside the brain substance. This difference in site is doubtless to be attributed to the rarity of vascular degenerations in childhood. Of the 50 cases of haemorrhage 1 was extradural, 11 were subdural, 16 were subarachnoid, 16 were cerebral, 4 were cerebellar, and 2 were in the brain stem. Eight of the intracerebral haemorrhages resulted from embolism during the course of malignant endocarditis and one was associated with chronic nephritis.

These figures, if representative, suggest that if these diseases can be excluded an intracranial haemorrhage in a child is twice as likely to be outside the brain as in its substance. This fact, when coupled with the difficulties of clinical diagnosis, leads us to believe that if a child has an acute progressive intracranial lesion and the C.S.F. is clear, there is no alternative to exploration of the subdural space on one or both sides, even if this policy results in a certain number of unnecessary operations.

Summary

A case of acute subdural haematoma occurring in infancy is described.

Difficulties in diagnosis are discussed.

It is shown that a child with symptoms and signs of a progressive intracranial lesion and with a clear C.S.F. should be regarded as an immediate surgical problem, even in the absence of a history of trauma.

We are grateful to Dr. E. Mackworth for permission to publish the case.

REFERENCES

Aring, C. D., and Merritt, H. H. (1935). *Arch. intern. Med.*, **56**, 435.
Ingraham, F. D., and Matson, D. D. (1944). *J. Pediat.*, **24**, 1.
Sheldon, W. P. H. (1927). *Quart. J. Med.*, **20**, 353.
Storch, T. J. C. von, and Munro, D. (1938). *New Engl. J. Med.*, **218**, 6.

The need for varied and interesting play material for very young children is stressed in a new booklet—*Play with a Purpose*—published by H.M.S.O. for the Ministry of Health (price 1s.). It has been written mainly to help and advise those in charge of groups of young children in nurseries, and shows the value of simple play material in helping the all-round development of the child. Pictures of the type of toys most suitable to the child at various stages of his development are accompanied by many useful hints.

A CASE OF HYPERSENSITIVITY TO PETHIDINE IN A WOMAN IN LABOUR

BY

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Pethidine was first introduced as a spasmolytic and analgesic drug by Eisleb and Schaumann (1939). Since then the pharmacology and clinical possibilities of the drug have been fully investigated. Among its other uses pethidine has been found to be of great value as an analgesic in labour. This was first described by Benthin (1940); since then other workers have confirmed the importance of pethidine in this field, so that now it is probably the most widely used analgesic in labour, and can be given by midwives on their own responsibility.

The comparatively mild toxic effects of pethidine are always given favourable emphasis in accounts of the use of this drug. In animals, however, with the use of larger doses per kilogram than in man, pethidine causes hypotension, respiratory depression, and bradypnoea. In very large doses apnoea may occur (Gruber, Hart, and Gruber, 1941). In man a marked transitory fall of blood pressure also occurs, within three to four minutes, when the drug is given intravenously, and a moderate fall, maximum in 40 minutes, when given by intramuscular injection. This was reported by Branwood (1943), but in his series no alarming symptoms were noticed.

Cases have been described in which pethidine has caused a more severe reaction—e.g., apnoea, severe hypotension, or collapse—but these have occurred after giving it by intravenous injection. Therefore it seems of interest to record the following case of hypersensitivity to pethidine in a woman in labour, in which the drug was given by intramuscular injection.

Case History

A married woman aged 24 was admitted in labour at full term on January 2, 1951. She had felt well throughout her pregnancy, which had been quite normal. Labour began at 1.30 a.m. on January 2, and the patient was admitted to hospital at 6.30 a.m. On admission the clinical findings were as follows: B.P. 120/80; urine, N.A.D.; height of fundus, 40 weeks; presentation, vertex L.O.A.; head engaged; foetal heart heard; pains 1 in 10. On rectal examination the cervix was 3 cm. dilated. Pethidine, 100 mg., was given by intramuscular injection at once.

Labour progressed normally, and the cervix was fully dilated at 8.50 a.m. The patient was then encouraged to bear down with the pains. At 9.40 a.m. she suddenly became cyanosed and developed a transient urticarial rash on face, abdomen, thighs, and legs in quick succession. The rash had disappeared from the face by the time it appeared on the legs. She complained of feeling faint. The pulse was imperceptible, and the blood pressure could not be recorded. Until this time the foetal heart had been heard, but five minutes after this attack began she delivered normally a fresh stillborn male infant. The placenta and membranes followed 20 minutes later.

After delivery the blood pressure still could not be recorded, and the urticarial rash appeared again on the face, with some oedema of the lips and eyelids. This gradually disappeared, and by 10 a.m. a weak pulse could

be felt, and the blood pressure was 70/?. Her condition continued to improve, and by midday the blood pressure was 120/80 and her condition satisfactory.

The child was a boy weighing 7 lb. 4 oz. (3.29 kg.). At necropsy no abnormality was found except some congestion of the liver.

A careful history was taken. The patient had never had any similar attack before. On the previous day she had eaten her normal diet and taken nothing unusual. She did not find that any food "disagreed" with her. During labour she had nothing to eat, and drank only tea and water. With the exception of pethidine, only gas-and-air analgesia was used.

It was therefore felt that the reaction was probably due to pethidine, and the following test was carried out with the patient resting in bed. The blood pressure was taken and 50 mg. of pethidine was given by intramuscular injection. Blood pressure readings were taken every half-hour for six hours.

Time	B.P.	Remarks
10.15	120/75	
50 mg. pethidine given I.M.		
10.45	120/80	
11.45	110/75	
12.15	110/70	
12.45	110/70	
1.45	110/80	
2.25	90/60	Marked puffiness of face. "Drawing" feeling in skin
2.40	90/65	No puffiness of face
3.10	105/70	
4.00	100/65	

In the test the maximum fall in blood pressure of 20 mm. Hg systolic and 15 mm. Hg diastolic occurred four hours after the injection of pethidine. During labour, collapse occurred 3¼ hours after the pethidine injection.

It seems reasonable to conclude from the results of this test that the reaction during labour was caused by pethidine. The case also demonstrates that, even with normal dosage of a commonly used and usually safe drug, unexpected and serious reactions may occur, endangering the lives of both mother and child.

I would like to thank Dr. Jeffery Jones, medical superintendent, for permission to publish this case, and Dr. J. Graham, lecturer in pharmacology, Welsh National School of Medicine, for his assistance and advice.

REFERENCES

Benthin, W. (1940). *Dtsch. med. Wschr.*, **66**, 760.
Branwood, A. W. (1943). *Edinb. med. J.*, **50**, 177.
Eisleb, O., and Schaumann, O. (1939). *Dtsch. med. Wschr.*, **65**, 967.
Gruber, C. M., Hart, E. R., and Gruber, C. M., jun. (1941). *J. Pharmacol.*, **73**, 319.

According to the latest annual report of the Medical Defence Union, membership of the Union on July 17, 1951, stood at 35,700 practitioners. It is noted that the Medical Act, 1950, which is now law, has introduced changes in the mode of conduct of disciplinary cases before the G.M.C., and it has been decided to open membership of the Union to the newly qualified during the intern year they must do before they are permitted on the *Medical Register*. During the year 1950, 2,135 cases were conducted, among them one where a member with an emergency commission in the R.A.M.C. was posted as commanding officer of a hospital and gynaecological specialist, but was not promoted to temporary major, the rank held by his predecessor. The War Office at first refused to grant him higher status and pay, but the solicitors to the Union were able to show that the military authorities had wrongly interpreted their own regulations, and he secured his promotion.

HERPES ZOSTER WITH INVOLVEMENT OF ANTERIOR HORN CELLS

BY

J. H. McINTYRE, M.D.

(From Grey Hospital, Greymouth, New Zealand)

The following case may be of interest, as motor disturbances are rarely seen in herpes zoster.

Case Report

A man aged 40 was admitted to hospital on May 8, 1950. He complained of an irritating rash on his inguinal region and buttocks of the left side. He gave a history of having been in hospital a week previously for a lacerated face, for which he received prophylactic injections of penicillin. While in hospital he felt an irritation in the skin of the left buttock and extending round to the inguinal region and lower abdomen in front. Shortly after discharge he noticed a rash on those areas. He had never been in contact with chickenpox so far as he knew.

Examination showed that he was a middle-aged man of rather nervous temperament. His temperature was 100.2° F. (37.9° C.), pulse 90, respirations 20. He had a typical herpes zoster involving the left buttock behind, the left inguinal region in front, and also the suprapubic region, the segments affected being the first to third lumbar. It is perhaps noteworthy that the herpetic vesicles passed slightly beyond the midline of the lower abdomen for a distance of ¼–1 in. (1.25–2.5 cm.).

The vesicles were painted with collodion and he was given 1 ml. of pitressin daily for three days. The vesicles dried up satisfactorily, but on May 15 he complained of pain on the medial side of the left thigh in its upper third, and there appeared to be some loss of power in the left leg. The next day the knee-jerk and ankle-jerk were absent, as also was the plantar reflex. He complained of considerable pain in the whole of the quadriceps and medial side of the thigh on movement. There was also ½ in. (1.25 cm.) of muscular wasting. There was no fibrillary tremor.

Lumbar puncture showed no increase of pressure, and clear fluid was obtained. On examination this was found to contain 62 cells per c.mm., of which 56 were lymphocytes and 6 polymorph leucocytes. There was a slight increase of globulin by Pandy's test.

The haemoglobin and red-cell counts were normal, and the white-cell count was 9,700 (neutrophils 68%, lymphocytes 28%, monocytes 3%, eosinophils 1%).

On May 18 the patient had more marked paresis of the left leg, with absent reflexes and pain on attempted movement. By May 25 he was completely paralysed in the left leg, with loss of all tendon reflexes and 1 in. (2.5 cm.) of muscular wasting. He had severe pain on passive movement. He was anaesthetic in the areas where the herpetic vesicles had been present—that is, in the area supplied by the first to third lumbar segments.

By June 2 movements in the affected limb were slowly beginning to return, and by June 18 he could move the limb a little and the ankle-jerk had returned, the plantar reflex was flexor, but the knee-jerk was still absent. There was, however, still pain on movement.

This was thought to be a case of virus infection of the anterior horn cells of the first to third lumbar segments, which had spread over from the posterior horn cells or the posterior root ganglia, where it had caused a typical herpes zoster.

The similarity to acute anterior poliomyelitis was, however, striking, and the results of lumbar puncture rather supported this diagnosis; on the other hand, the paralysis was not maximal in onset, but came on very slowly. In addition, there was no neck or spinal rigidity, and this district has been free from poliomyelitis for a considerable time.

Discussion

Broadbent in 1866 was the first to describe a case of herpetic eruption in the course of branches of the brachial plexus followed by partial paralysis in corresponding motor nerves. Since then relatively few cases have been observed, although much interest has been shown in this condition. Taterka and O'Sullivan (1943) reported two cases of zoster with motor complications—one affecting the upper limb and the other the lower. They stated that they had been able to collect from the literature 42 cases of herpes zoster with motor complications. In an analysis of these cases they note that the total number of cases is 44, and that the proportion of males to females is almost 3 to 1. They further state that paralysis of the muscles of the upper extremity occurred in 20 patients, or 45.5% of the cases. The trunk muscles were affected in 18 cases, or 40.9%, and, including their own two patients, there have been only six cases of paralysis of the muscles of the lower limb. They further state that the zoster eruption precedes the paralysis in about three-fourths of the cases and follows it in only one-fourth. The time interval between the eruption of the herpes zoster and the appearance of the paralysis varies from one day to two months. The eruption and the paralysis never appear simultaneously.

In the case under discussion the interval between the appearance of the herpetic eruption and the paralysis was precisely 14 days. Furthermore, there was a history of trauma in this case, but the relation of trauma to the aetiology of herpes zoster is problematic. It occurred in several cases in the literature, but no conclusive result is forthcoming.

The pathogenesis of herpes zoster is not well understood. It is usually stated that there is an inflammatory reaction of the dorsal root ganglia caused by a filterable virus, but how this virus arrives at the dorsal root ganglia is not known. Kinnier Wilson (1940) stated that it travels by the blood stream from the nasopharynx to the spinal ganglia, where it induces tissue reactions and then moves along the sensory nerves to the skin, producing a segmental eruption.

Other observers consider the disease to be an ascending neuritis. As regards the motor complications in herpes zoster it seems logical to assume that this is spread by continuity from the spinal ganglia to the anterior root. Kinnier Wilson, however, denies the existence of lesions of the anterior root and considers a spread of the virus among cell groups of ventral horns more likely.

Herpes zoster has been described as the sensory analogue of poliomyelitis, and the virus of zoster always attacks the sensory system, but the case here described and the other 44 cases mentioned give reason for thinking that the anterior horn cells or motor roots can also be affected. Whether there is any different strain of virus or type of virus that causes these uncommon motor complications can only be conjectured. Several observers have described these motor complications of herpes zoster as acute posterior poliomyelitis, and certainly the clinical findings and cerebrospinal fluid changes support this description.

Summary

A case is described of motor paralysis complicating a herpes zoster, the muscles affected being the quadriceps femoris and the vastus medialis.

The occurrence of this complication in the lower limbs is uncommon, only six previous cases having been reported.

The interval between the herpetic eruption and the onset of the paralysis was 14 days.

The distinction of this condition from acute anterior poliomyelitis can be difficult, as the cerebrospinal fluid changes are similar in both diseases, but the paralysis is of more gradual onset in the motor complications of herpes zoster.

I am indebted to Dr. R. H. Quentin Baxter, of Christchurch, for literature and advice on this subject.

REFERENCES

Broadbent, W. H. (1866). *British Medical Journal*, **2**, 460.
Taterka, J. H., and O'Sullivan, M. E. (1943). *J. Amer. med. Ass.*, **122**, 737.
Wilson, S. A. Kinnier (1940). *Neurology*, edited by A. Ninian Bruce. Arnold, London.

Medical Memorandum

The Pneumatic Balance Valve and its Applications: a Preliminary Report

The pneumatic balance (P.B.) valve is a device for transforming a continuous gas pressure into an intermittent one. A P.B. valve interposed between a low-pressure source of oxygen, controlled by a suitable pressure regulator (demand valve), and a rubber bag will inflate the bag to approximately three-quarters of the pressure to which the demand valve has been set (the line pressure), and then cut off the oxygen and allow the bag to deflate through ports provided for this purpose. When the residual pressure of the gas in the bag has dropped to a predetermined value (say one-tenth of the line pressure) the process is again reversed and the valve continues to cycle so long as the line pressure is maintained.

FIG. 1.—The pressure balance valve.

The valve (Fig. 1) consists of a circular metal box, some 2½ in. (6.3 cm.) in diameter, with inlet and outlet connexions. The internal mechanism consists of two diaphragms linked together, which cover valve seatings of different diameters. The smaller valve controls the inlet of fresh gases; the larger valve is on the outlet side of the apparatus, and, owing to its mechanical advantage over the smaller one, to which it is linked, shuts off the flow of gas and opens the expiratory ports when the pressure in the bag reaches three-quarters of that of the demand valve.

Although first described in 1945 in the United States, the P.B. valve does not seem to have received much attention in this country, which is surprising because

of its numerous clinical applications, simplicity, small size and outstanding advantages.

The simplest clinical application of the P.B. valve is automatically to inflate the lungs of a subject in need of artificial respiration. Interposition of the P.B. valve between a demand valve, set to deliver oxygen at the desired pressure, and an air-tight face-mask is all that is required.

Since the valve is pressure-operated, the time of cycling (respiratory rate) will depend on the size of the lungs and the pressure applied to the valve. Thus it will be seen to cycle more quickly when applied to a child than when used on an adult. Also, since pressures developed by any attempt on the subject's part to breathe affect the balance of the valve, it will tend to fit its cycling to any respiratory efforts.

It has been stated above that a slight positive pressure remains in the lungs at the end of the expiratory phase of the valve (about one-tenth of the line pressure); this has a certain clinical value, since it may prevent (or cure) any tendency to pulmonary oedema.

The simple apparatus described above, while perfectly satisfactory on the unconscious patient or the patient with complete respiratory paralysis, tends to be resented by the conscious patient and the patient capable of voluntary respiratory effort. Although it is possible voluntarily to stop an inspiration, it is not possible to accelerate it, as the speed at which the valve operates is a function of its design and the gas pressure applied to it. This results in a feeling of suffocation. A more elaborate apparatus (Fig. 2) overcomes this defect by placing a second demand valve in parallel with the first. This second valve is adjusted so that there is no gas flow except during a voluntary inspiration. It is connected to the facepiece through a "Y" connexion, the other limb of the Y being attached to the P.B. valve. In this way automatic artificial respiration is achieved, with the addition of unlimited supplies of gas "on demand" should the patient make a gasping inspiratory effort.

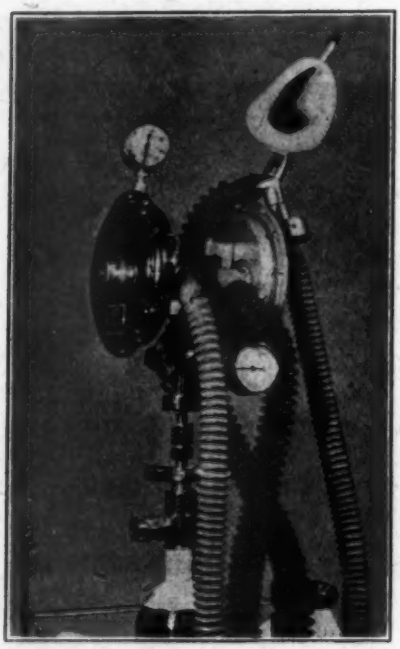

FIG. 2.—Showing two demand valves in parallel. The P.B. valve can be seen just below the face mask on the extreme right.

In anaesthesia, the interposition of a P.B. valve between apparatus of the intermittent-flow type (McKesson) and the patient will give satisfactory controlled respiration. When it is desired to use the valve with the absorption technique it has to be applied indirectly. The bag of the absorber unit is enclosed in a rigid case (Fig. 3), and the P.B. valve controls gas (or air) pressure exerted on the outside of the bag, and in this way causes a rhythmical compression of the breathing bag.

Apart from its application to anaesthetic technique, this valve should prove of great value in cases of poliomyelitis with respiratory paralysis when the patient is removed from the cabinet type of respirator for nursing, etc.; indeed, it has already been used for this purpose in place of manually operated inflators. The latter are not popular with patients owing to inherent defects in hand operation, the difference between one operator and another, and a feeling of suffocation if the control is operated too slowly.

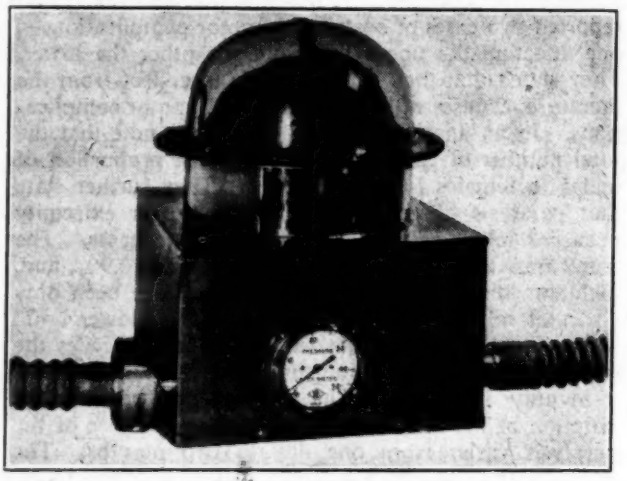

FIG. 3.—Using the P.B valve indirectly to apply pressure to the outside of a bag attached to an anaesthetic circuit. The P.B. valve is on the left. The tube on the right is attached to the anaesthetic circuit.

In the field of resuscitation a respirator of the type illustrated has many possibilities. As a therapeutic device for post-operative pulmonary complications and depressed respiratory centres the valve affords a new line of treatment. As a means of obtaining and maintaining controlled respiration in anaesthetics it is most promising.

For experimental work and the development of prototype apparatus in connexion with this valve I am indebted to the unfailing co-operation and enthusiasm of Mr. E. P. Childerhouse, of Medical and Industrial Equipment Ltd., London, W.1.

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BIBLIOGRAPHY

Burns, H. L. (1945). "Pneumatic Balance Resuscitator," *Air Surgeon's Bull.*, **2**, 306.

Motley, H. L., Cournand, A., Eckman, M., and Richards, D. W., jun. (1946). "Physiological Studies on Man with Pneumatic Balance Resuscitator 'Burns Model,'" *J. Aviation Med.*, **17**, 431.

—— —— Werko, L., Himmelstein, A., Dresdale, D., Johnson, R., Lester, M., Spierto, B., and Richards, D. W., jun. (1946) "Physiological and Clinical Studies of Intermittent Pressure Respirators and Manual Methods for Producing Artificial Respiration in Man." Memorandum Report, T.S.E.A.A. 696-79-f. A.A.F. Headquarters. A.M.C. Engineering Division, Aero Medical Laboratory, Wright Field.

—— —— —— Dresdale, D. T., Himmelstein, A., and Richards, D. W., jun. (1948). "Intermittent Positive Breathing: A Means of Administering Artificial Respiration in Man." *J. Amer. med. Ass.*, **137**, 370.

Reviews

ACROSS THE ATLANTIC

William Shippen, Jr., Pioneer in American Medical Education. By Betsy Copping Corner. A Biographical Essay. With notes, and the original text of Shippen's Student Diary, London, 1759–60; together with a translation of his Edinburgh Dissertation, 1761. Memoirs of the American Philosophical Society, Volume 28. (Pp. 162; 9 figures. $2.75.) Philadelphia: American Philosophical Society. 1951.

In the years preceding the American War of Independence the links between the American Colonies and the Mother Country were close and friendly. This was especially the case with medicine, and, as there were then no medical schools in America, many medical students crossed the Atlantic to take a British qualification. Dr. Archibald Malloch, in his FitzPatrick Lectures for 1939 on "Medical Interchange between the British Isles and America before 1801," has given an account of these students and of the welcome they received from the leaders of the British medical profession. Firm friendships were forged between masters and pupils—a happy state of affairs which through the influence of Osler, Harvey Cushing, and others has been revived and strengthened in our own times. These pioneers carried the torch of British medicine back to America and founded the early American medical schools on British practice. The first of them was William Shippen, Jr., the subject of Mrs. Corner's biographical essay.

William Shippen the younger was born at Philadelphia in 1736. After a course in arts at the College of New Jersey (now Princeton), he studied under his father (pupil of the elder Kearsley) and went to London in 1759. From mid-July to January 22, 1760, he kept a diary, which is printed in the biography and carefully annotated by Mrs. Corner. It gives an interesting picture of people, places, customs, and events in mid-eighteenth-century England, and introduces us to a hard-working, pleasing, and moral society which compares favourably with parts of that recorded in Boswell's *London Journal*, written a few years later.

Shippen studied obstetrics under Dr. Colin Mackenzie at the United Hospitals of St. Thomas's and Guy's, saw Percival Pott operate at St. Bartholomew's Hospital, and attended William Hunter's Anatomical School. In October, 1759, he became an inmate of John Hunter's house in Covent Garden, where, after attending lectures, dissecting, and injecting anatomical specimens all day, he often "talk'd anatomically with Mr. Hunter" until bed-time. He made friends with Dr. Fothergill, Dr. Mark Akenside, the poet-physician, and Benjamin Franklin, danced with "pretty and genteel young ladies" at assembly rooms, and admired Garrick in tragedy and comedy.

The diary ends too soon, but we learn from Mrs. Corner that William continued his studies at Edinburgh, graduated as M.D. in 1761 with a thesis *De Placentae cum utero nexu*, of which a translation is given, married Alice Lee, of Virginia, the sister of Arthur Lee, who was United States Commissioner with Franklin in Paris during the War of Independence, and returned to Philadelphia to teach anatomy, obstetrics, and surgery, and to found the first medical school in America.

During the War of Independence, Shippen was appointed Director-General (1777–1781) of all the military hospitals of the American armies. Temperamentally he was unfitted for administration, and his work was adversely criticized and attacked by John Morgan and Benjamin Rush. Shippen demanded a court-martial, which acquitted him. Three months later he resigned his appointment and returned to teaching and practice in Philadelphia.

In 1791 he saw his medical school become a part of the University of Pennsylvania, and in 1798 he retired from practice. He said in his last address to the students in 1807 that he could now depart in peace, as he had seen the completion of his labours for the medical school. He died in 1808, and his old foe, Benjamin Rush, attended him on his death-bed.

Mrs. Corner, as editor of William Shippen's diary and as his biographer, has given us a revealing study of a medical student in London in the eighteenth century. It will be read with equal appreciation on both sides of the Atlantic.

ARTHUR S. MACNALTY.

PANCREATIC SECRETIONS

The External Secretion of the Pancreas. By Professor J. Earl Thomas, M.D. American Lecture Series Publication No. 45. (Pp. 149; 22 figures. £1 5s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1951.

This little monograph is number 45 of the American Lecture Series, of which the editor of the physiology lectures is Professor Robert F. Pitts, of Cornell. The editor, and the publishers, have every reason to be proud of this excellently produced series, of which the present is a good example, for the general production standard is high and is here well maintained.

The author has himself done careful and fruitful work on the subject, and the book bears the imprint of a master hand and a critical mind. The subject being a relatively circumscribed one, he has found it possible to treat it in a rather leisurely and scholarly way, which, with his own attractive modesty, makes the book a pattern of what a monograph can be. The references are well chosen and the illustrations well selected. If one could find a fault, it is with the use of the term "ecbolic" to connote stimuli which, while causing no visible secretion alone, increase the enzyme content of the juice in response to coincident "hydrelatic" stimuli. Despite the fact that this term was coined by the late Professor Babkin, it seems a pity to use a word which has another quite different, though obsolescent, meaning. Perhaps a new word is needed to replace the old word "trophic" of blessed memory, and no doubt the Greeks have a word for it, but is "ecbolic" that word?

C. LOVATT EVANS.

NEUROLOGY FOR STUDENTS

The Neurologic Examination. Incorporating the Fundamentals of Neuroanatomy and Neurophysiology. By Russell N. DeJong, M.D. (Pp. 1,079; 368 illustrations. £5 10s.) New York: Paul B. Hoeber, Inc. London: Cassell and Co. 1951.

It is difficult to know for what type of reader this book has been written. The text is said to be based on "the lectures on the neurologic examination given to junior and senior students" in the author's medical school, but few medical students in Britain would have the time or inclination to read the 1,033 pages of concentrated information. The author discusses in considerable detail the methods of clinical neurological examination, but, good as the descriptive writing is, it

is a poor substitute for bedside instruction, which is surely the way to teach methods of examination. The author correlates the disturbance of function and the abnormal signs of disease with the anatomy and physiology of the nervous system, but says little about pathology or differential diagnosis apart from the problems of localization of cerebral and spinal lesions. In successive chapters he considers the various parts of the central, peripheral, and autonomic nervous system, and there are also chapters on the examination of stuporose patients and on the examination of patients suspected of hysteria or malingering. Special methods of examination such as neuro-radiology and electro-encephalography are not considered, but there is a chapter on examination of the cerebrospinal fluid. It is rather surprising in a book of this size that there is no account of quantitative vestibular tests. This book will be a necessity for the collector of eponyms (for example, the syndromes of Garel and Gignoux, of Gerhardt and of Marin Amat), of unusual terms (pallanesthesia as a synonym for loss of vibration appreciation), and of unorthodox reflexes (the little toe reflex of Puussepp).

The book is well produced, the references for further reading are well chosen, and the illustrations, clinical photographs, and anatomical diagrams are clear. But it is a pity that a picture on p. 291 showing a unilateral palatal palsy is said to be taken from a book by S. J. Purves on the *Diagnosis of Nervous Diseases*, when it is in fact from Sir James Purves-Stewart's famous book of that name.

J. W. ALDREN TURNER.

ALCOHOL AND DRIVING

Alcohol and Road Traffic. Proceedings of the First International Conference. Edited by R. Wagnsson, K. Bjerver, G. Nelker, S. Rosell, and J. Akerbladh-Rosell. (Pp. 336. 15 Kronor.) Stockholm: Kugelbergs Boktryckeri. 1951.

Twenty-two countries took part in this conference, which was held during August 30 – September 1, 1950, at Stockholm under the patronage of the King of Sweden. It was recognized that the occasion was only a first step taken to survey the ground and obtain a clearer idea of the problem of alcohol and road traffic. It was thought that constructive action on a broader basis could be effected later by continuing international co-operation. The book records essential parts of the medical, legal, and educational communications and the subsequent discussions.

Reports from the participating countries give valuable information about the provisions adopted to deal with such problems as the method of ascertaining the presence and degree of intoxication; the extent to which blood and other chemical tests, clinical tests, medical opinions, and statements of witnesses and police officers are used; and whether a record of sobriety is a condition of receiving a driving licence. Other matters concerning the licence holder's record are considered, as well as propaganda activities against the consumption of alcohol when driving motor vehicles.

Medical articles consider the significance of tolerance (L. Goldberg), estimation of the level of blood alcohol from analysis of breath (R. N. Harger, R. B. Forney, and H. B. Barnes), an indirect method of determining alcohol in blood using samples of breath (H. W. Smith), a comparison with the Widmark method of the determination of ethyl alcohol by crystallized alcohol dehydrogenase (K. Bjerver, R. K. Bonnichsen, L. Goldberg, and H. Thorell), quantitative analysis of alcohol in the blood by heat reaction (E. Shifferti), the effect of alcohol ingestion on driving ability (K. Bjerver and L. Goldberg), accident contributions of drivers as a function of their blood levels (H. W. Smith and R. E. Popham), and risks of ambiguity in dealing with and solving problems connected with alcohol and traffic (P. Dauphin). The articles are admirably constructed and well documented. The legal articles include studies from the U.S.A., Sweden, Norway, Belgium, and Denmark and deal with various approaches to the subject. It appears that alcohol tests are compulsory only in the Scandinavian countries, in Czechoslovakia, and in certain cantons in Switzerland. The last part of the book is on economic, pedestrian, insurance, temperance, and statistical aspects of the problem. A good index is provided.

This is a unique and valuable contribution to a socially important subject. Workers in this field will constantly refer to it.

W. NORWOOD EAST.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

In a Harley Street Mirror. By R. Scott Stevenson. (Pp. 278. 15s.) London: Christopher Johnson. 1951.

The Great Plague in London in 1665. By W. G. Bell, F.S.A., F.R.A.S. (Pp. 861. 25s.) London: The Bodley Head. 1951.

Second Sight. By L. Spence. (Pp. 190. 18s.) London: Rider. 1951.

Birch's Management and Medical Treatment of Children in Tropical Countries. By E. H. Vere Hodge, C.I.E., B.A., M.D., F.R.C.P., F.S.M.F. 9th ed. (Pp. 412. Rs. 16.) Calcutta: Thacker, Spink and Company (3, Esplanade East, Calcutta). 1951.

Handbook of Medical Management. By M. Chatton, A.B., M.D., and others. 2nd ed. (Pp. 507. $3.) California: University Medical Publishers. 1951.

Thyreotoxikosen und antithyreoidale Substanzen. By Professor H. W. Bansi. (Pp. 99. M. 11.40.) Stuttgart: Georg Thieme. 1951.

Sensibilitätsschema. By Professor K. Hansen. 2nd ed. Part A: *Segmentäre Innervation.* (Pp. 50. M. 4.80.) Part B: *Periphere Innervation.* (Pp. 50. M. 4.80.) Stuttgart: Georg Thieme. 1950.

Dr. K. G. Khorozian, author of *The Microkaryocytes, the Fourth Corpuscles and Their Functions* (Boston: Meador Publishing Co.; $12), is a physician with a general practice in the village of Pineville, West Virginia, who carries on biological research in his spare time. He describes, under the name of microkaryocytes, hitherto unknown corpuscular elements from which the entire structural make-up of all living organisms, both animal and plant, is formed. They are said to be cells with distinct nuclei and cytoplasm. It is claimed that the metabolism of the body is accomplished through the media of these newly discovered cells. The various naturally occurring granules—pigment granules, haemokonia, blood dusts, mitochondria, inclusion bodies, elementary bodies, etc.—are the same and identical bodies, the microkaryocytic cells. "All enzymes are cells, all hormones are cells," and the crystallization of enzymes and hormones is dismissed as a myth. The author has used the principle of enlargement by projection, as used in the moving-picture industry, which is very different from orthodox methods of resolution of fine structure. The first public announcement of the author's views was made at the meeting of the American Medical Association in June, 1944, and they do not seem to have achieved wide acceptance.

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EARLY TREATMENT OF POLIOMYELITIS

In last week's *Journal* (p. 669) we reported a discussion about the treatment of poliomyelitis at the second International Congress held at Copenhagen earlier this month. There are so many stages in the treatment of this disease that it is difficult to present an account of the whole picture. The first phase of the illness (the "minor illness") appears in only half of the cases and consists of a catarrhal disturbance which has no specific features and lasts for about 24 hours. No special treatment is required, but during epidemics minor symptoms of this kind should not be entirely ignored, and physical fatigue should be avoided for about 10 days after any such incident, since this probably reduces the likelihood of the dangerous "major illness" developing.

The development of the meningitic stage ("major illness," pre-paralytic stage) is abrupt in over 80% of cases. Here the virus is engaged in certain phases of multiplication, which were vividly described at the Copenhagen conference. Some of these critical phases, which must be developing at the onset of meningitic symptoms, occur within periods of a few hours. It is by no means impossible that before long some substance will be discovered which, when given to the patient at this stage, will have an indirect action on the virus through an effect on the host cell. This, however, is a hope for the future. In the meantime the patient should be treated with the greatest care in the early hours after the onset of meningeal symptoms, for it is at this stage that the fate of the nerve cells is decided. The virus has by then been in the motor cells for several days and is embarking on its most dangerous phases. Complete physical rest is the most valuable known method of reducing the nerve-cell vulnerability at this time, but it must not be delayed. Even a few hours of average activity (such as shopping, or going to school) during this early stage seems to affect motor-nerve-cell metabolism in such a way as to lessen the cell's chance of survival. Experimentally it has been found that cortisone has the opposite effect and lessens cell resistance to the poliomyelitis viruses.

The development of meningitic symptoms naturally causes great alarm to all concerned, but it is most important that the patient should be surrounded by an atmosphere of calm and efficiency; sedation with barbiturates and analgesics should not be withheld, for restlessness and anxiety may do harm. When considering infectivity, the doctor should bear in mind that several members of the house and neighbourhood are probably already excreting virus in the stools and are just as infective as the patient. Since, however, less than one case in a hundred develops paralysis it is most improbable that more than one member of a small circle will develop a dangerous illness: those with abortive infections will develop a useful life-long immunity to the disease. Therefore any suggestion of rushing the patient away to protect others is unreasonable in poliomyelitis, and the doctor need consider only the patient's interests when deciding whether he should go to hospital. There is much to be said for the view that the pre-paralytic phase should be spent quietly in bed at home, especially if the journey to hospital is likely to be a tiring or frightening ordeal, but circumstances vary, and, of course, meningitis must be excluded. Lumbar puncture may be performed at home, but patients who develop disturbance of consciousness should certainly go to hospital for accurate diagnosis.

The development of paralysis requires a reassessment of the situation, for disasters may occur very quickly. The first danger to consider is the development of difficulty in swallowing due to the bulbar type of the disease. Secretions collect in the pharynx and cause a characteristic bubbling rattle with every breath. In this event the patient should at once be turned on his face and the foot of the bed raised about 2 ft. (60 cm.) to allow secretions to drain out of the mouth and throat by gravity: he should be kept in this position while being moved to hospital. Mechanical aspirators should always be available for these cases, but must be used gently. Such patients should always be "specialled" in hospital, and the nurses who look after them must be given appropriate training. The other grave danger is the spread of paralysis to the muscles of respiration. This is recognized by a quickening rate of respiration, by loss of strength to cough, by the visible feebleness of chest and diaphragm movements, and especially by the inability to say more than one or two words with each breath (tested by asking the patient to count). A few days spent in a respirator to rest weak muscles will probably lessen the amount of permanent paralysis, hence all such patients should be transferred to a hospital where the staff is experienced in respirator treatment. Unfortunately it cannot be

said that the fever hospitals in either this or other countries are properly staffed to handle these difficult problems, and there is anxiety in all countries about the gaps in the organization for the early treatment of poliomyelitis.

There are some wide divergences of opinion about the early treatment of paretic muscles, owing largely to the unfortunate absence of accurate physiological data about the pattern of muscle recovery in this disease in varying circumstances. It is to be hoped that this information will be collected by research workers before long.

The interesting new work on the virus of poliomyelitis was fully discussed at the Copenhagen conference, as reported on another page in this issue. Thanks to the success in growing human strains of poliomyelitis virus on tissue cultures the treatment and prevention of the "major illness" is likely to show some great advances during the next few years. Mr. Basil O'Connor, president of the National Foundation for Infantile Paralysis, reported at Copenhagen on the activities of the Foundation, and said that the income from voluntary subscriptions in the U.S.A. for 1950 was thirty million dollars. The extremely expensive virus research which the Foundation, with commendable vision, decided to support, is now beginning to bear fruit in a manner which must be highly gratifying to all concerned. Though it must be admitted that we still do not know how to prevent or cure poliomyelitis, we are learning fast about its natural history and mode of spread, and we know of some things which make it worse and can be avoided. New knowledge of the existence and distribution of three antigenic types of poliomyelitis virus should lead to a better understanding of the disease, and prospects of prevention by active and passive immunization are now in better perspective. There are even faint rays of hope in the field of chemotherapy. If the rhesus monkey can be replaced by the roller tube in the laboratory, there are good hopes of making swift advances before the next congress in 1954.

ASPECTS OF FLYING

The jet aircraft demonstrated at Farnborough last week were a further reminder that flight at high speed and high altitude is now a commonplace. This is true not only in military aviation but also in civil air transport, for "Comet" airliners flying at 40,000 feet and over 500 m.p.h. are going into service with B.O.A.C. Constant high speed has no physiological effects in itself, though changes of speed (acceleration or deceleration) are another matter; and course-plotting at 10 miles a minute makes new demands on the mental agility and reaction time of navigators and pilots, whose nerve impulses will always travel at less than half this speed. But high altitude, and the speed with which it is reached, involves many medical problems, which must for the most part be solved by designers, physiologists, and engineers before the aircraft ever leaves the ground, and therefore can only become a traveller's concern if there is an accident during flight. At 40,000 feet the temperature is a freezing Arctic cold of about −55° C. Since this height can be reached in a few minutes after take-off from a ground temperature of as much as 38° C. the aircraft must have extremely good ventilation and cabin heating to maintain a comfortable internal air temperature of 20° C.; or very complete clothing, especially electrically heated gloves and shoes, must be worn.

At 40,000 feet the atmospheric air pressure is less than one-fifth of normal.[1] This has two kinds of consequences. Breathing is ineffective because the low pressure only drives a very feeble draught of air into the lungs as they are expanded by the respiratory movement, and in any case the partial pressure of oxygen is too low to ensure full oxygenation of the blood. But the mere decrease in pressure, especially if rapid, brings other physiological disasters. Gas trapped in the intestines will expand rapidly to five times its volume at ground level, causing great abdominal pain and distension unless it can somehow escape promptly by mouth or anus. Nitrogen dissolved in the blood may come out as small bubbles in various tissues when the pressure is greatly reduced: "bends" or decompression sickness, with acute pain and sometimes paralysis, is the result. These ill effects are prevented by pressurization: the air inside the aircraft is maintained at four-fifths of normal atmospheric pressure, equivalent to an altitude of 8,000 feet, at which the oxygen pressure is quite adequate and no physiological difficulties are likely to be encountered except in some cases of disease, especially of heart and lungs.[2] Alternatively oxygen masks and special pressure suits must be provided for each individual, who will guard against gas-producing foods in his diet, and may breathe pure oxygen for a spell before take-off to wash the nitrogen out of his blood.

These are obvious and well-known matters on which extensive research was done between 1939 and 1945. But the protective effect of the atmosphere has been less studied. At 40,000 feet cosmic radiation is about one hundred times more intense and approaches

[1] Bergin, K. G., *Aviation Medicine*, 1949. John Wright, London.
[2] Whittingham, H. E., Barbour, A. B., and MacGown, J. C., *British Medical Journal*, 1949, **1**, 603.
[3] Schaeger, H. J., *J. Aviat. Med.*, 1950, **21**, 375.
[4] Barr, N. L., ibid., 1950, **21**, 328.

the tolerance dose for radiation; at greater heights it may even exceed the safety level.[3] There is much more ultra-violet light in the sunlight, but the glass or perspex of windows should effectively filter it out. The lack of clouds to scatter and diffuse the sunlight makes it a harsh glare nearly ten times brighter than at ground level, with the general sky brilliance cut to one-fifth and intense black shadows in the aircraft, so that the pilot has difficulty in reading his instruments, and the usual relations of dark and light are reversed—brilliant white clouds below and an inky black sky above and around. "It is like flying in a bowl of bright milk with a black Wedgwood cover."[4] The design of instrument dials for these conditions becomes a matter of the applied physiology of vision, just as cockpit design in general has become a problem for applied psychologists to determine the best layout and shape for the multitudinous controls which the pilot must learn to handle almost instinctively, especially in emergency.

A great deal of air safety, however, now depends on administrative action rather than scientific inquiry. Passenger seats all facing backwards have proved their worth in R.A.F. crashes, when the occupants have merely been rammed further into the upholstery, instead of being thrown violently forward and having their necks broken. Elsewhere in this issue Dr. Donald Teare draws attention to the risk that the standard safety belt worn with the forward-facing seat may frequently rupture the abdominal aorta in the event of a crash, a further argument for fitting aft-facing seats. A proposal is now before the International Commercial Aviation Organization that all civil airliners should adopt this safer seating plan, which would involve at the same time re-stressing the flooring of most commercial aircraft; and consequently the airline corporations are somewhat reluctant to make the change. But it is now being increasingly realized that the limits of flight are the physiological limitations of man and not the restrictions imposed by engineering practice, and aircraft are gradually coming to be designed with medical requirements in mind. Modern aviation medicine can do much to improve the performance of the crews of present-day military aircraft, but it will have to go far before the interplanetary flights envisaged by the international astronautical congress recently held in London become humanly practicable.

LEPTOSPIROSIS

The world-wide distribution of leptospiral infections and the various forms which they manifest in their clinical, bacteriological, and epidemiological aspects make their study one of particular interest, and this interest has perhaps been enhanced by the confusion which originally existed in the differential diagnosis of yellow fever and Weil's disease. In the present issue of the *Journal* Dr. J. C. Broom gives an exhaustive review of the subject, with particular emphasis on the occurrence of the two forms—Weil's disease and canicola fever—which have so far been recognized in England and Wales. In different parts of the world there are other leptospiral infections of importance: for instance, in the North Caucasus, Australia, Palestine, and the U.S.A. there is a disease in bovines due to *L. bovis* which is transferred to human beings through infected milk.

Dr. Broom has been particularly well placed for this investigation, since from 1947 his laboratory became the Leptospiral Reference Laboratory of the Public Health Laboratory Service, and within the period under review no less than 465 cases of Weil's disease and 54 cases of canicola fever have been investigated. It is possible that more cases could have been discovered if there was a greater awareness of the disease and if further facilities were provided for accurate bacteriological diagnosis. In the past many bacteriologists have been reluctant to undertake the examination of specimens, but the technique of culture and the examination of serum for agglutinins and lysins present no insuperable difficulties. The proper timing of the specimen is of course important, for the leptospira are present in the blood stream during the first four or five days, and the agglutinins begin to appear on the sixth day or later. Specimens of urine to be examined for leptospira should be recently obtained.

For the treatment of Weil's disease the only agent available until recently was a specific antiserum, and this form of therapy was of value only if given early on in the disease before the fifth day. Now, however, the antibiotics in everyday use have been proved by animal experiment to inhibit and effectively abort infections with *L. icterohaemorrhagiae* and *L. canicola*, and presumably they would be equally effective against the various other types of leptospira. Broom discusses the treatment of human infections with antibiotics, and a further contribution to this subject has been made recently by Dr. C. W. Lawson.[1] Broom's analysis shows that there appears to be no benefit to be derived from giving penicillin even in large doses. The reason for this is probably twofold. In the first place, young patients develop a less severe form of the disease than the elderly and seem to make a complete recovery without difficulty. Secondly, the disease is usually bacteriaemic only during the first four to five days after the onset, and it is during this period that the damage to the tissue of the body, particularly the kidneys, occurs. To be effective, therefore, the antibiotic should be given within a day or so of the onset of the illness: this postulates an immediate clinical diagnosis, since the bacteriological confirmation will not be available until some days later. Even though the results of Broom's analysis have been disappointing, the practitioner suspecting a leptospiral infection should proceed with antibiotic therapy, prescribing the dosage usually recommended for any acute infection. Nineteen per cent. of the patients in Broom's series contracted Weil's disease while bathing, and in the miscellaneous group were a number of cases in which no obvious

[1] *British Medical Journal*, 1951, 2, 648.

source of infection could be traced. But, in so far as occupational infections are concerned, Weil's disease could be prevented by the measures which Broom describes.

PELVIC EXENTERATION

Despite new methods of diagnosis, the majority of cases of uterine cancer, particularly of cancer of the cervix, are in one of the later stages when first diagnosed. In addition, some of the earlier cases may fail to respond to surgery or radiation and eventually advance to a later stage. For these patients Wertheim's operation is inadequate, and the results of radiotherapy are not unexpectedly poor. Within the last few years the possibilities of extremely radical surgery for the advanced case have been examined, and Brunschwig, the pioneer in this field, described his results in 78 cases at the twelfth British Congress of Obstetricians and Gynaecologists in July, 1949.[1] He had previously given an account of 22 cases of advanced genital cancer in the female treated by the operation of complete pelvic exenteration.[2] This procedure entails the abdomino-perineal resection of the pelvic lymph nodes, bladder, rectum, and entire genital tract, together with colostomy and transplantation of ureters. The operation obviously provides a formidable exercise in surgery, but it can achieve successful results. Notwithstanding the advanced stage of the cancer Brunschwig often found his patients to be in surprisingly good general condition. His surgical mortality amounted to 25%, but this may be justified, for he was able to report apparent cures in patients previously regarded as certain to die. Only when there was clinical evidence of extra-pelvic metastases did he not attempt operation, which was abandoned if laparotomy showed periaortic lymph-node deposits or peritoneal or hepatic spread.

Stimulated by Brunschwig's example, Parsons and Bell[3] sought to confirm whether radical surgery offers a reasonable hope of cure of advanced pelvic cancer and of a tolerable life thereafter, and they have reported their results in 29 women—24 of them suffering from carcinoma of the cervix. This growth is considered the most suitable for extensive surgery, because even in the terminal stages the cancer is still confined to the pelvic viscera and glands in about 40% of cases. In this series spread of cancer to the lymph nodes was demonstrated in only 32% of the patients at laparotomy. The cases selected for operation were those so far advanced when first seen that radiotherapy could offer only palliation, those found by biopsy or smear examinations to be resistant to radiotherapy, and those with extensive recurrence after radiation. Seven of the 29 women died in hospital within four weeks of operation, a surgical mortality of 24%. Another seven had at the time of report returned to their previous occupation for from 12 to 16 months after operation, while recurrences occurred in only four of the eighteen women who had left hospital.

It is apparent from this report and from another analysis of the same material[4] that survival after operation largely depends on the state of the urinary tract and on renal function. Apart from the possibility of pre-existing disease, the kidney is affected by the shock of operation and by the loss of protein from the huge denuded area in the pelvis. Therefore close attention must be paid to the sodium and electrolyte balance. The management of urinary complications requires sound judgment, and in six of ten patients dying in hospital the cause of death was lower nephron nephrosis. Parsons and Bell found that convalescence was smoother with skin ureterostomy than with ureterocolostomy, and the former was preferred if pyelonephritis was present or if the renal reserve was low. Complete pelvic exenteration is not always necessary, and in fact Parsons and Bell found it possible to conserve the rectum in three and the bladder in two of their patients. Brunschwig and his associates[5] have also reported a series of 36 cases of female genital cancer involving the bladder for which the partial operation was performed, the bowel being spared. Of the first 21 patients, 4 were alive and well for periods varying up to two years at the time of report. Six of the 21 women died within four weeks of operation, but there were only 2 such deaths in the last 15 cases. None of the deaths occurred during the operation. It appears to have been established that patients can survive this radical surgery and resume a useful and reasonably normal life.

CORONARY DISEASE IN THE COMMUNITY

The great increase in deaths attributed to coronary-artery disease in the last 25 years is as well known as it is perplexing. Morris,[1] for instance, has shown that advanced coronary atheroma actually decreased while deaths from coronary thrombosis and myocardial infarction increased. The natural history of coronary disease in the years 1921–45 was reviewed by Ryle and Russell,[2] whose combined clinical and statistical investigation clarified some aspects of the disease, only to bring further problems to light. As D. D. Read[3] pointed out at one of the Festival Symposia recently, there has probably been much switching of diagnostic labels in the last 30 years, but fundamentally the disease is probably not the expression of a changing fashion in diagnosis, of a premature ageing of arteries, or of the changing age distribution of the population. Although predominantly a disease of males, particularly in the younger groups, an even more marked characteristic is that it is a disease of the professional classes. The highest mortality is among physicians and surgeons. In discussing the aetiological possibilities Ryle and Russell examined the conditions of work and the strains in many professional and business careers which, if endured too long, might become beyond physiological tolerance. Some

1 *Trans. XIIth Brit. Cong. Obstet. Gynaec.*, 1949, London, p. 248.
2 *Cancer*, 1948, **1**, 177.
3 Ibid., 1950, **3**, 205.
4 Parsons, L., and Leadbetter, W. F., *New Engl. J. Med.*, 1950, **242**, 774.
5 *Amer. J. Obstet. Gynec.*, 1950, **59**, 237.

1 *Lancet*, 1951, **1**, 13 and 69.
2 *Brit. Heart J.*, 1949, **11**, 370.
3 *British Medical Journal*, 1951, **2**, 113.
4 Stocks, P., *Lancet*, 1951, **1**, 351.
5 Rentoul, E., ibid., 1951, **1**, 587.
6 *The Listener*, 1950, **43**, 872.
7 *Lancet*, 1950, **2**, 867.

have argued that under-exertion of the body may be a more important aetiological factor[4 5] than over-exertion of the mind. It might be added that overwork is more often a symptom of overstrain than a cause; and the emotional factor emerges again as one of the features of the disease. As Thomas Hardy wrote, more life trickles out through a man's thoughts than through a gaping wound.

Coronary disease appears to result from a pathological adaptation to stress. Although the problem can be stated in terms of Heberden's "disturbance of mind" and of ischaemic heart muscle, its solution, like that of other stress diseases, can also be sought in a more philosophical concept, perhaps such as that of Demant,[6] who described a sickness of the community "in which the multifarious contacts of recent times grow to a point at which the human being cannot adapt himself without spiritual and mental and often bodily sickness." In elaborating this idea Stewart[7] attempted to show that the ambitious person who strives to achieve independence is at the present time subject to a new form of stress for which recent social changes are responsible. The social historian of the future will perhaps write about the present rise and recognition of the stress diseases. In at least one of them he may well wonder why doctors, whose profession was to teach patients how to adapt to their circumstances of life, were themselves most commonly the victims.

PETHIDINE IN ANAESTHESIA

Dr. W. B. Neff, of San Francisco, introduced pethidine into anaesthetic practice in 1947, and two years later Drs. W. W. Mushin and L. Rendell-Baker published in this *Journal* the first British paper on this use of the drug.[1] Since then pethidine has become as common in the anaesthetic room as in the obstetrical wards. It is used as a substitute for morphine in pre- and post-operative medication, particularly when vomiting is expected or has to be carefully avoided, and it is administered intravenously during operation instead of the usual adjuvants to nitrous-oxide anaesthesia. Repeated small doses of thiopentone are often given for this purpose, and it is with this drug that pethidine is most often compared. Both are respiratory depressants, but pethidine has the shorter action; it does not produce the troublesome long narcosis after operation so common after large doses of thiopentone, nor does it provoke laryngeal spasm; restlessness and other after-effects are slight, though pethidine in out-patient anaesthetic practice causes vomiting and giddiness in some patients as soon as they are allowed to get up to return home.

Elsewhere in this issue Dr. P. Dunbar Johnson describes his experiences with pethidine in more than 200 operations. He established anaesthesia with thiopentone and maintained it with nitrous oxide in a circle absorber, giving gallamine triethiodide to achieve muscular relaxation when necessary. The average patient required an initial dose of 50 mg. of pethidine and a further 20 mg. every 20 minutes after that; a more uniform level of anaesthesia was obtained and less pethidine had to be injected when it was given by intravenous transfusion at the rate of 1 mg. a minute. Johnson found that a solution diluted to 5–10 mg. per ml. for intermittent intravenous injection or to 0.2 mg. per ml. for continuous administration by intravenous transfusion had no significant effect on the respiration. He describes his results as good in comparison with other forms of anaesthesia, and he praises the rapid return to consciousness, the absence of respiratory depression, the bronchial relaxation, and the prolonged post-operative analgesia afforded by his technique. Another paper in this issue, by Dr. E. Blanche Butler, emphasizes that pethidine is not free from its own dangers. She reports a patient, later found to be hypersensitive to pethidine, who suffered a severe fall in blood pressure and oedema of the face after 100 mg. had been given by intramuscular injection during labour: the effect of a smaller dose given by intravenous injection to a similar patient in the operating theatre might have been more serious.

[1] *British Medical Journal*, 1949, 2, 472.

ALCOHOLISM AND ADRENAL INSUFFICIENCY

Evidence is accumulating that adrenal cortical hormones play a part in cerebral metabolism, especially in connexion with glycogen and glutamic acid, and some authors have discussed the possibility that abnormal mental states may be associated with deficiencies in these hormones. Hoagland, who with his collaborators has done much work on this subject, has even put forward evidence to show that an electrically induced convulsion causes the release of adrenal corticotropic hormone into the blood, the implication being that this is the *modus operandi* of electro-shock therapy.[1] The relation of the adrenals to alcoholism is even more interesting. Tintera and Lovell[2] maintain that there is a constitutional syndrome which goes with excessive susceptibility to alcohol. It shows itself in an asthenic habitus, hypotension, a soft, smooth face, and hairlessness of the chest, sometimes even gynaecomastia, and, at the biochemical level, in hypoglycaemia and low values of 17-ketosteroids and androgens—all signs attributable to hypo-adrenocorticism. While the alcoholic may not be burdened from the beginning with a constitution of this type, by heavy drinking he may damage the adrenals and develop it. Then, by a vicious-circle mechanism, the low blood sugar might continue to stimulate the desire for alcohol. For the treatment of such a syndrome adrenal cortical extracts would seem to be indicated. Smith[3] advances an even more comprehensive theory. He points out that Celtic and Scandinavian peoples are the most susceptible to alcoholism, the Semitic and Chinese peoples least. Genetic rather than ethnic differences might account for this. The alcoholic presents both physical and mental qualities which are to some extent distinctive and suggest hypo-adrenalism. Baldness occurs about 10 times as frequently in the general population as among alcoholics, who, in Smith's experience, are usually single or

separated from their wives, and, if married, have small families. Socially they lack responsibility and are poor workers. The peak incidence of the severest forms of alcoholism is in the early forties, the beginning of the male climacteric. Smith believes that alcoholism can be regarded as a metabolic disease, being led to this view by the similarity between delirium tremens and an Addisonian crisis. In both conditions plasma potassium and nitrogen are increased, sodium and chloride decreased; and dehydration, acidosis, and, often, a low blood sugar accompany the other signs. "The biochemical, clinical, and therapeutic similarities of these two disease states are so striking that the existence of identical pathological processes must be presumed." Deficiency of pantothenic acid can cause haemorrhage, necrosis, and lipoid depletion in the adrenals; and the biochemical changes in the blood consequent on pantothenic acid deficiency bear many resemblances to those of alcoholism and Addison's disease. It has, of course, long been considered probable that much of the disability caused by alcoholic addiction occurs through vitamin depletion.

These theoretical views have led to a series of therapeutic experiments, which Smith has reported in a second paper.[4] The patients included sufferers from Korsakoff's psychosis, acute alcoholic intoxication, and delirium tremens, and the effect of giving adrenal cortical extract (A.C.E.), desoxycorticosterone, testosterone, and adrenocorticotropic hormone (A.C.T.H.) was observed. Both A.C.E. and A.C.T.H. gave good results in 80 patients suffering from acute alcoholic intoxication. A.C.E. seemed to be the better of the two, but with both drugs the degree and rapidity of the improvement could not be equalled by standard methods of treatment. On the other hand, A.C.T.H. appeared to be more effective than A.C.E. in the 46 patients with delirium tremens. One of the interesting findings which appears from the tables accompanying Smith's paper is that in the more refractory conditions, the Korsakoff state and delirium tremens, not all the symptoms are benefited equally and with the same speed. Disorientation, especially in time, outlasts such other symptoms as hallucinosis, restlessness, tremulousness, sweating, and fear.

These theories and the methods of treatment which have sprung from them are not without rivals in the field. The treatment of alcoholic intoxication and delirium tremens with insulin in sub-shock doses, together with abundant fluids and vitamin-B complex, is very effective, as recent communications bear witness.[5-7] Other biochemical theories—one, for instance, incriminating anoxia—have been proposed. But the adrenal hormone theory is in the centre of the picture, not least perhaps because medical interest is so strongly focused on this aspect of endocrinology.

[1] Hoagland, H., Callaway, E., Elmadjian, F., and Pincus, G., *Psychosom. Med.*, 1950, **12**, 73.
[2] *Dig. Neurol. Psychiat.*, 1949, **17**, 521.
[3] *Quart. J. Stud. Alcohol.*, 1949, **10**, 251.
[4] Ibid., 1950, **11**, 190.
[5] Tillim, S. J., *Amer. J. Psychiat.*, 1944, **101**, 396.
[6] Vassaf, E. G., and Hall, V. R., *New Engl. J. Med.*, 1946, **235**, 190.
[7] Thimann, J., and Peltason, P., *Quart. J. Stud. Alcohol.*, 1947, **7**, 506.

PROTEST AT EAST GRINSTEAD

The attempt of the Ministry of Health to lay hands on £24,000 subscribed to build a children's wing at the East Grinstead Queen Victoria Hospital has aroused great indignation in the locality, and indeed elsewhere. A public meeting[1] was held on September 17, at which Sir Archibald McIndoe protested against the "unhappy situation suddenly precipitated by which East Grinstead might lose two things it could not do without—a children's ward at the hospital and a collecting organization known as the Peanut Club." The money now in the fund was collected from many thousands of people before and during the war to build a children's wing at the hospital, which has won international renown for its achievements in plastic surgery. During the war many Servicemen were treated there, and much of the money was in fact subscribed by members of the Services. According to Sir Archibald McIndoe the trustees of the fund offered it to the Ministry in 1949 for the specific purpose of erecting a children's wing, the need for which was urgent, and the offer was accepted. Nothing more was heard for 18 months; then suddenly a letter was received from the Ministry calling upon the trustees to hand over the money so that it could be transferred to the hospital endowments fund.

This central fund was established under Section 7 of the National Health Service Act, 1946. Under the Act all money voluntarily subscribed to non-teaching hospitals before the passing of the Act is to be transferred to the hospital endowments fund. The Minister is therefore bound to claim the money for the fund, as he points out in the letter that was read at the meeting. Whether the same sum, or any sum, would thereafter be made available for building a children's wing is problematical: during the debate on the N.H.S. Bill Mr. Bevan described this kind of money as "pocket money."[2] But Mr. Marquand offers some hope that an equitable solution may be found when he says the Ministry is investigating how, within the framework of the Act, the money may be put to the purpose for which it was subscribed. However satisfactory the Act may have been in the power it gave to deal with some types of endowment, there are exceptional cases such as that at East Grinstead. We have previously drawn attention to another—the unhappy fate of the Sanderson-Wells Prize for nurses.[3]

The procedure of claiming funds given voluntarily for specific purposes, transferring them to a general pool, and then distributing sums of money as Ministry officials think fit must appear to many—and so it was described at East Grinstead—to be plain robbery. As we go to press the Ministry has issued a statement saying that as a result of the transference the hospital will be better off and it will have its new wing no less quickly. But whether all the money is to be applied to building the new wing still seems to be questionable.

[1] Reported in the *Supplement* at p. 117.
[2] *British Medical Journal*, June 1, 1946, p. 860.
[3] Ibid., August 12, 1950, p. 406.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

EARLY RECOGNITION OF CONGENITAL DEFECTS

BY

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Infants with congenital defects may be grouped as (*a*) those presenting an obvious anatomical lesion at birth—for example, cleft-lip or mongolism; (*b*) those presenting an anatomical lesion not immediately recognizable but discovered by routine examination—for example, congenital heart disease and imperforate anus; (*c*) those presenting with a functional disorder resulting from an anatomical defect the recognition of which may be delayed until the organ in question is put to the functional test—thus in oesophageal atresia vomiting will occur after the very first feed, a short oesophagus may not be recognized until later, and a congenital defect of the hip may not be diagnosed until the child attempts to stand; and (*d*) those presenting with an anatomical lesion made manifest by the onset of infection or, more rarely, of malignant change—for example, infective endocarditis and malignant change in an ectopic testis.

However, with the recent advances in our knowledge of the causation of some of the congenital defects an alternative grouping from the aetiological point of view might be (*a*) those of hereditary or familiar aetiology—for example, achondroplasia and acholuric jaundice; (*b*) those due to noxious influences on the developing foetus—for example, maternal rubella and toxoplasmosis; (*c*) those due to intrauterine influences—for example, some cases of talipes; and (*d*) those due to maternal dietetic deficiencies, evidence for which is largely in the animal experimental stage.

Thus it might be said that some defects can be expected, some suspected, and that others are latent. If the practitioner is to prepare himself for the possibility of a baby having a congenital defect he must take a full antenatal history, make an adequate antenatal examination of the foetus as well as of the mother, and undertake a complete examination of the newborn baby.

Antenatal History

In taking the history there are two main lines of inquiry, the first into the family stock, and the second into the health of the mother. The family history must elicit the presence of any congenital defects in members of the families of both parents and information about their consanguinity. If blood relations marry there is a greater risk that both partners may be carriers of a recessive gene. A sex-linked defect may be revealed, for example, by a history of pseudohypertrophic muscular dystrophy in the male members of the mother's family.

Since the work of Gregg and Swan in Australia it seems to be well established that rubella occurring in the first three months of pregnancy may cause harm to the developing foetus, with subsequent disorder of its growth and development leading to such conditions as cataract, deafness, and possibly congenital heart disease and cerebral agenesis. This discovery has opened a vast field for exploration, but so far no other virus disease in the mother has proved to be a responsible factor for congenital defects; nevertheless the conception of foetal damage as the result of a maternal viral infection must be regarded as established. The probability of one of the defects, particularly cataract or deafness, following maternal rubella in the first three months of pregnancy is high, and some obstetricians have even suggested that it is an indication for terminating the pregnancy. To justify this, however, there must be no doubt of the diagnosis of rubella and the infection must be within the first three months. Even then it should be remembered that the only legal indication for terminating is related to the health of the mother and not to the health of the foetus.

Another condition which, though rare in this country, leads to foetal changes is toxoplasmosis due to a parasitic involvement of the developing nervous system. The mother is the carrier of the disease and is usually unaware of its existence; when active in the early weeks of pregnancy the disease has been found to be responsible for such states as microcephaly, hydrocephalus, intracranial calcification, and eye changes. Skin testing may detect the condition in the mother in early pregnancy, but unfortunately there is no known method of treating this state of affairs.

It seems fairly well established from experimental and clinical evidence that radium or deep *x*-ray therapy applied to the uterine field during the early weeks of pregnancy may result in the baby being born with an anatomical defect affecting particularly the skull and nervous system.

Maternal dietetic deficiencies have not so far been shown to be clearly related to foetal abnormalities in man, but in animals on deficient diets, especially of vitamins A and D and riboflavin, foetal changes have occurred, and although these results may not be strictly applicable to human development they at least suggest a possible cause of defect which needs further study. In this respect iodine deficiency has long been known to play a part in the causation of cretinism in the baby.

The age of the mother and her parity must also be noted, for they may have some bearing on the possibility of a congenital defect. The classical example of this, though there are many exceptions, is the mother of a large family who produces a mongol at the end of her child-bearing age.

Finally, antigenic incompatibility, especially to the rhesus factor, though not producing any direct developmental change, may result in such conditions as kernicterus and familial cirrhosis of the liver, which in the past were thought to be due to direct genetic causes. The occurrence of previous pregnancies or miscarriages, or of jaundice or anaemia in the babies, should therefore be noted and the mother should be asked whether she has previously had any blood transfusions.

Antenatal Examination

It should be remembered that congenital defects are commoner in abnormal presentations, in premature

births, and when hydramnios is present. In examining the mother, therefore, attention should be directed to these points. A persistently abnormal lie should call for a radiological examination, which, with good films and expert interpretation, may show such changes as anencephaly, achondroplasia, or other bony dyscrasias. If a gross abnormality of this sort is discovered the practitioner may be well advised to warn the parents that he is not altogether happy about the future of the child or he may prefer to pass the problem on for a specialist opinion.

Congenital heart disease may be suspected and sometimes diagnosed with confidence if a murmur is heard in the foetal heart sounds, though it is impossible to be certain of the exact lesion. Thyrotoxicosis has been diagnosed in the foetus with a very rapid heart rate in a severely thyrotoxic mother, but such diagnostic feats are few and far between.

Immediate Examination of the Newborn Baby

Examination of the newborn baby is sometimes perfunctory, and indeed after a difficult midnight delivery the doctor may well postpone a detailed examination until the morning. He should, however, satisfy himself that no immediate catastrophe is imminent from any congenital defect and that no obvious deformity will be found by the mother before him. As a first measure he should note the presence or absence of cyanosis and determine its cause in relation to the heart. As a second measure he should determine, so far as is possible, that the alimentary tract is patent. This may not be easy, but if the baby has not passed meconium he should look to see that the anus is open, for an imperforate anus calls for immediate attention. Other obstructive conditions in the alimentary tract may not manifest themselves until feeding is begun. Finally he should look inside the baby's mouth, otherwise he will miss a cleft-palate and his reputation may not unnaturally suffer.

Detailed Examination of the Baby

In the more systematic examination it is useful to start with the skull, for more frequently than elsewhere in the skeleton the skull shows changes in its shape, and such conditions as microcephaly may indicate an underlying cerebral agenesis. The general shape and size of the skull should be noted and also the character of the sutures and fontanelles. The maximum circumference of the normal skull is 13½ in. (34.3 cm.), but its shape may be temporarily modified by the caput succedaneum. The posterior fontanelle is normally almost closed, but the anterior fontanelle is open, with the sutures easily palpable. The size of the anterior fontanelle in particular and the width of the sutures may vary considerably within normal limits.

The abdomen needs careful palpation, though inspection in a good light is often more informative. Most causes of intestinal obstruction which need surgical relief will give rise to vomiting, visible peristalsis, abdominal distension, and failure of bowel action. If obstruction is suspected, as it may well be if vomiting persists from birth, a straight *x*-ray film of the abdomen and a study of the air shadows are more helpful than a lipiodol swallow and should always be done first.

A newborn baby's first feed should be carefully observed. Sudden distress, with cyanosis and frothing at the mouth, suggests an oesophago-tracheal fistula, which calls for immediate surgery. It is the wise practice in many nurseries for the newborn to be given only sterile water or saline for the first feed, until the continuity of the oesophagus has been established.

Cyanosis, which may be cerebral, respiratory, or cardiac in origin, requires careful classification. If of cerebral origin it will tend to vary and to be accompanied by a greyish colour in a shocked ill-looking baby, and there may well be other cerebral signs such as twitching or stiffness of the limbs, a tense fontanelle, and vomiting. Cyanosis of respiratory origin will vary with the crying of the baby and improve with oxygen therapy : on the other hand cyanosis of cardiac cause will be more constant, will not respond much to oxygen, and will tend to increase when the child cries.

It is by no means uncommon for a baby with cyanotic heart disease to have no audible cardiac murmurs ; this is sometimes forgotten. Persistent deep cyanosis is seldom due to anything but congenital heart defects. Although murmurs may be absent, often the heart sounds are tick-tack in character and the heart rate is rapid. Cyanosis and recession of the ribs during inspiration are more important as an indication of the severity of the condition than the presence or absence of a murmur. The common systolic murmur of a non-cyanotic heart lesion, especially those due to septal defects, is often missed at birth because its harshness and timbre are almost identical with that of the breath sounds in a newborn baby. It therefore requires careful listening to separate and distinguish such a bruit.

The genitalia need careful inspection, and the site and patency of the anus and urethra must be determined. The pseudo-hermaphrodite may suddenly develop a suprarenal crisis with vomiting and collapse, and such cases should not be dismissed too lightly as a future problem for the plastic surgeon. Most minor degrees of defect in the male, such as hypospadias, are best left for surgical repair until the child is older, but the mother must be told the reason for delayed treatment. In the female an ectopic anus may not be noticed at first, but it is best dealt with as soon as the child's feeding is established and she is gaining weight satisfactorily, but before mixed feeding is begun.

Most limb deformities are obvious and visible—for instance, polydactyly or syndactyly—but dislocated hips may pass unobserved for some time. Talipes, which in some cases, especially of the equino-varus type, is probably due to intrauterine posture, needs early treatment, and these cases should therefore be referred to an orthopaedic surgeon within the first two weeks. Talipes associated with a meningocele and spina bifida is a different problem, for then the integrity of the nervous system, as judged by the muscle tone of the legs and the shape of the skull, is the overriding factor in determining the treatment. Most meningoceles are best left without surgical removal for at least a year, and this is certainly so if the lower limbs are flaccid.

Examination of the eyes and ears is difficult but important. Such defects as cataract or retrolental fibroplasia in premature babies may easily be missed unless carefully looked for. Deafness is impossible to detect in the early months. As a rule it is delay or difficulty in speech that first arouses the mother's doubt about her child's hearing, and it is surprising how late parents may be in suspecting this disability. It is often more helpful to watch the mother unconsciously using sign language to her child than to watch the child.

There are, in addition to gross structural changes in particular organs, certain general congenital conditions which may be recognizable at birth. The most important, perhaps, of these, because it is the most frequent, is mongolian idiocy, which unlike cretinism can and should be diagnosed at birth in almost every instance. There is still no known cause for this tragic condition, but it would seem by analogy that it might be due to some noxious influence on the foetus in its early development. However, no direct evidence for this has been forthcoming, and we are still left with the view that it is related to chromosome changes associated with the age of the parents as the only clue to its aetiology.

Latent Defects

There are many congenital heart lesions that pass unnoticed until later in life, as every school medical officer can testify. Most of the children with these lesions are without symptoms of their disability, as, for example, those with a patent ductus arteriosus or the rarer coarctation of the aorta. These are commonly first found at routine examination, and so far as these two particular defects are concerned the first is usually missed because the child is not undressed and the stethoscope does not reach the pulmonary area, and the second is missed because the femoral arteries are not palpated as a routine. A patent ductus is relatively common and has assumed greater importance because it can be cured by ligation. The optimum age for this is between 7 and 9 years, but if there are symptoms of distress at an earlier age there is no need to delay surgery. The development of infective endarteritis is an immediate indication for operation. In this country we have hardly had enough experience of the surgical treatment of coarctation of the aorta in children to be able to lay down an optimum operation age, and decision must depend in each case on such factors as the symptoms, size of the heart, blood pressure, etc.

Perhaps the most difficult of the latent defects to recognize is mental deficiency. In cases associated with obvious physical signs, such as in mongols, there is seldom difficulty, but in others an associated physical defect may either not be recognized or its significance not be appreciated. In such cases there may also be difficulty in distinguishing the congenital or genetic defects from those that are acquired or due to environmental influences, as in some instances of cerebral palsy. In order to find these defects as early as possible the doctor must keep the newborn baby under frequent review, especially noting for this purpose his developmental progress. Gesell's studies have greatly helped us to appreciate the early developmental delays and deviations that portend poor mental progress.

Just as some congenital defects are recognized only by careful routine examination, others force their attention on the doctor by some functional or symptomatic disorder, often precipitated by infection. There are many examples of this; for instance, the development of infective endocarditis is the signal that there has been an underlying but latent congenital heart lesion; or an intractable diarrhoea and spasmodic cough in a baby with a good appetite but a coeliac contour suggest that the disease is due to congenital cystic changes in the pancreas and a congenital genetic dysfunction of the mucus-secreting glands. Other examples of conditions in which infection first attracts attention to a congenital defect are cystic changes in the lungs or kidneys, for so long as infection is kept at bay quite gross deformity may pass unnoticed. It is true to say, especially of boys, that a persisting urinary infection nearly always indicates some congenital abnormality of the renal tract, and an intravenous pyelogram will probably be needed to disclose it.

What to Tell the Parents

Finally, it may be helpful to discuss the very practical problem of when and how much a practitioner should tell parents when he suspects or finds a congenital defect. This is never an easy decision to have to make. If the family history in this respect is a bad one the mother may already have had her suspicions aroused, and it is then as well to warn her if these suspicions are justifiable, for if the doctor is right in his prognostications the mother will be less disturbed by their realization and will be more able to accept the inevitable, but if he is wrong then she surely will be delighted. As in all comparable situations the way in which the news is likely to be received depends on the temperament and intelligence of the mother and father and on the manner of its telling by the doctor. However, if at birth a congenital defect is obvious the doctor should have no hesitation in presenting the known facts. If he is in doubt about the extent or significance of the findings he may justifiably modify his statement until the findings have been confirmed, but it is kinder to the parents, and it will earn him greater respect in the end, if he tells them of his suspicions as soon as he can. It is never an easy task for either party, but its tactful and smooth achievement may make all the difference to the future of the family.

Thus it will be seen that congenital defects may present themselves in the antenatal period, or immediately or soon after birth, or they may not be manifest for some years. The doctor should always be on the alert to detect them, for not only may some of them be amenable to surgery but with their recognition the child's life can be adjusted accordingly and the family life and happiness, so often in jeopardy when a deformity is found, safeguarded and preserved.

In an article in the *Journal of the American Medical Association* (August 25, p. 1589) Dr. John Flumerfelt draws attention to some of the problems raised when a physician wishes to refer a patient to a psychiatrist. Apart from the rather suspicious attitude towards psychiatrists still adopted by many otherwise well-informed people, there are certain other difficulties mainly arising out of the psychological effect that such a decision may have upon the patient, who may, for instance, think that "neurosis" means insanity, or that there is some weakness of character implied by the need for psychological treatment. On the whole these objections are made up of feelings of guilt, caused by impulses of which the patient is unaware Even when the patient agrees to undergo such treatment the presence of these feelings must be borne in mind. Many patients require some help from the referring physician, and he is obviously the person best qualified to help, as he knows most about the patient. Dr. Flumerfelt stresses the importance of always telling the patient that the doctor to whom he is being referred is a psychiatrist, however opposed to this he may know the patient will be; if he does not tell him it is likely that the patient will erect such a defence against the psychiatrist that nothing will be achieved. Much delicacy must be exercised by the doctor when he suspects that the trouble is of mental origin, or the patient's condition may easily be made worse. In fact, it must be remembered that psychotherapy has already been started when a patient goes to his doctor for help, and continues when the doctor advises him to see a psychiatrist.

COMMENTS ON THE USE OF RADIOGRAPHY IN DETERMINING THE PLACENTAL SITE

BY

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The time-lag between a discovery or an innovation and its acceptance and application in medicine is generally considerable. It took Lister twenty years to convince the London surgeons of the efficacy of antiseptics. More than a hundred years elapsed between the recommendation by Lebas in 1769 that the uterine wound should be stitched after caesarean section (Fasbender, 1906) and the adoption of this detail by Kehrer in 1881 and Sänger in 1882. Other instances in the obstetrical domain might be quoted: the tardy development of "antenatal care"; the hesitant adoption of rubber gloves and face-masks as a protection against infection; the reluctance to admit the superiority of the "lower segment" incision in caesarean section; the slow acceptance of radiography for mensuration of the pelvis.

But the advance to which I would particularly direct attention here is the sudden enthusiasm which has sprung up for the employment of radiography in the diagnosis of placenta praevia, as evidenced by two most important discussions—one at a meeting of the Obstetrical and Gynaecological Section of the Royal Society of Medicine on October 20, 1950, and the other at a joint meeting of this section with the Radiological Section on February 16, 1951. Nothing has cheered me up more, as I,

> "And like the vineyard worker take my way
> Down the long shadows of declining day,"

than this evidence of mental virility on the part of a number of the younger specialists in obstetrics and gynaecology.

It is fully twenty years since this particular advance was introduced. In 1930 Menees, Miller, and Holly described their method, which came to be designated "amniography." It consisted in injecting an opaque solution into the amniotic sac so that the placental site shows up as a filling defect. W. G. Mackay (obstetric consultant, Thornhill Hospital, Johnstone, Renfrewshire, but at the time my obstetric tutor) and I published our results with "uroselectan B" (iodoxyl) in 1933. The method was abandoned, as it occasionally resulted in inducing premature labour.

One day, while we were carrying out our experiments, Mackay, very thrilled at his discovery, showed me a direct or what has come to be referred to as a "straight" radiograph of the placenta *in situ*. It is this method which has come to be perfected in the United States and by Frank Reid, of the Department of Radiology in the Radcliffe Infirmary, Oxford,* under the inspiration of J. Chassar Moir (Munro Kerr and Chassar Moir, 1949) and J. A. Stallworthy (1951). To-day, exact and well-defined pictures of the placenta *in situ* can be secured by radiography.

Avoidance of Vaginal Examination

The advantage of employing radiography if placenta praevia is suspected is that by this method of diagnosis one can dispense with a vaginal examination. To push a finger or two fingers (frequently it is necessary to use both fore and middle fingers) through the cervix, even when great gentleness is employed, may result in further detachment of the placenta. On many occasions this examination has caused aggravation of haemorrhage to an alarming degree. Consequently, to-day the obstetric specialist carries out this vaginal examination only in the operating theatre and after he has made preparations for caesarean section or vaginal delivery in case that may be necessary.

It surprised me, however, in the recent discussions at the Royal Society of Medicine and in other debates in which radiography for diagnostic purposes has been under discussion—for example, pelvic formation—that a number of our obstetricians are timorous in advocating its free employment in obstetrics and give it rather half-hearted support. It is an advance of outstanding importance.

It is an extraordinary mentality, this reluctance on the part of many obstetricians to employ radiography freely to clarify diagnosis in obstetric complications. Physicians and surgeons take everything they can out of radiography; but a considerable number of obstetricians seem to imagine that by deprecating its free employment they place themselves on a higher platform of obstetrical intelligence. I read the other day a statement by a professor of obstetrics ("whole-timer") that "radiography was being much abused in obstetric practice." Of course it is, but not, I feel sure, by him and by other enlightened obstetricians. They possibly are not employing it freely enough.

I agree that from the clinical history and by abdominal palpation the experienced obstetrician can diagnose in many instances a placenta that is *praevia* and whether it is located on the anterior or posterior wall (an important detail, as Macafee and Stallworthy have stressed). But he cannot make certain which of the four degrees or types exists; and this also is of the highest importance when choice between vaginal and abdominal delivery has to be considered. I defy even the most skilled obstetricians to determine by palpation a placenta that is *praevia* in a stout multipara with pendulous abdomen. Vaginal examination excluded, only by radiography can one ensure the degree of exactness in diagnosis essential in making the choice of treatment most suitable for the particular patient under consideration.

This exactness in diagnosis should not result in an increase in the number of cases treated by caesarean section. In the hands of the expert obstetrician, well trained in both vaginal and abdominal methods of delivery, it should help him to balance the pros and cons for each route in cases in which one is not obviously indicated.

Other Advantages

But there is another advantage in employing radiography if the presence of placenta praevia is in question. Every now and again a malformed foetus will be recognized in the radiograph. Now, the proportion of malformed foetuses encountered in placenta praevia is roughly in the region of 4%. Of what profit is it to subject a patient in such circumstances to caesarean section when to-day, with blood transfusion, sulphonamide drugs, and penicillin, delivery by the vagina may be as safe for the mother—provided the obstetrician is equally well trained in both vaginal and abdominal techniques—as Sturrock (1947) pointed out in his important paper on placenta praevia?

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There's the rub. With the present swing-over to surgical methods many of the younger specialists have been starved of a training in the manipulations called for in complicated vaginal deliveries. Possibly this applies more in the smaller maternity units than in the larger maternity hospitals or maternity units of general hospitals; but we possess no information exact enough to justify a pronouncement on this point.

For many years the value of radiography as an aid to exactness in determining plural pregnancy, foetal malformations, intrauterine death, and pelvic formation has been recognized. Now we are witnessing its value in the diagnosis of placenta praevia. So let us be exceeding glad that this wonderful method of examination is now available in most large maternity units of general hospitals and in many large maternity hospitals throughout the country; and let us encourage other institutions to afford like facilities.

The dramatic drop in maternal mortality—a feature of the last two decades—can be maintained but not increased to a like degree in the future. The best one can hope for is that a small additional number of mothers may be saved by still more efficient antenatal and intranatal supervision.

Scope for Improvement

There is, however, scope for effecting a pronounced decrease in intrauterine, intranatal, and neonatal deaths, and in the incidence of premature births. All are much higher than need be. Recent results for placenta praevia are a specific illustration of what can be accomplished. Already the employment of radiography with the object of determining the degree or type of placenta praevia, the judicious use of expectant treatment, and the careful choice of mode of delivery (vaginal or abdominal) by a number of enlightened obstetricians have demonstrated what can be done to save the child—and, incidentally, to lower still further the maternal death rate.

I have pointed out the value of radiography in determining the placental site in cases in which placenta praevia is suspected, and also its value in determining pelvic formation. Now I put the question, "Is there any other condition in which a radiograph of the placenta *in situ* might be of advantage?"

One occurs to me. Should any difficulty be experienced in effecting version (external cephalic) in a breech presentation it might be advisable before proceeding further, and using force, to have a radiograph taken with the object of determining the placental site. A considerable number of obstetricians have this done as a matter of routine in breech presentations in order to exclude the possibility of any pelvic malformation. Here, however, I suggest it for the purpose of determining the placental site. Probably all of us have had the experience of an odd foetal death from detachment of the placenta following external version where it was effected with difficulty. It is just possible that this accident occurs almost exclusively in cases in which the placenta is situated on the anterior or antero-lateral wall of the uterus. In my earlier years in practice, when I was employing a classical incision in caesarean section, I came across the placenta in some 30% of cases.

Conclusion

I can hear readers of this article exclaim: "Really, when are these refinements in obstetrics going to end?" They are never going to end, for there is no finality in Medicine. That refinements in diagnosis and in treatment cannot be carried out in some outlying areas of the country is no argument against employing them where this is possible.

Permit me to finish this brief communication with a paragraph from the W. Fletcher Shaw Lecture ("The Investigation and Treatment of 'Borderline' Cases of Contracted Pelvis") I delivered in 1948 at the Royal College of Obstetricians and Gynaecologists (Munro Kerr, 1948). It rather pleased me at the time it was penned:

"I can hear some critics muttering that this investigation" [radiography of pelvis was the topic] "is too great a refinement. Don't listen to them. Look upon it as an example of the struggle which has gone on down through the ages to attain perfection. Emulate rather the anaesthetists, who seem never to be satisfied with their drugs, equipment, and contraptions, but are always striving after something better. And I admire their keenness and that they are not ashamed of showing it. Possibly this is because they have the exuberance of youth on their side, for their speciality is of yesterday, whilst ours had its beginnings in the primeval forests, jungles, and swamps millions of years ago and we may have grown weary in the long struggle."

REFERENCES

Fasbender, H. (1906). *Geschichte der Geburtshülfe*, p. 988. Jena.

Kerr, J. M. Munro (1948). *J. Obstet. Gynaec., Brit. Emp.*, **55**, 401.

Mackay, W. G., and Kerr, J. M. Munro (1933). *Edinb. med. J.*, **40** (Obst. Trans.), 21.

—— and Moir, J. Chassar (1949). *Operative Obstetrics*, 5th ed., p. 760. London.

Menees, T. O., Miller, J. D., and Holly, L. E. (1930). *Amer. J. Roentgen.*, **24**, 363.

Stallworthy, J. A. (1951). *Proc. roy. Soc. Med.*, **44**, 121.

Sturrock, J. (1947). *Edinb. med. J.*, **54**, 496, and quoted in *Operative Obstetrics*, p. 785.

SECOND INTERNATIONAL POLIOMYELITIS CONFERENCE

II. THE VIRUS AND ITS FELLOW TRAVELLERS

Some of those present at the first Congress, held in New York three years ago, felt that despite a vast expenditure of moneys and monkeys research was bogged down and that the future was not too hopeful. This year at Copenhagen, on the contrary, there was an atmosphere of optimism: useful leads were opening up in several directions.

Culture in Human Tissues

The most exciting was the work of Enders, Robbins, and Weller, described by Dr. J. ENDERS. They had succeeded in growing poliomyelitis virus in human embryo tissue-cultures, and, contrary to all expectation, had found that it would grow in all sorts of embryonic tissues, skin with muscle, and intestine, being as good as brain. Various adult human tissues, including foreskin, were also used with success. The Boston workers used essentially standard methods—suspensions of minced tissues (Maitland cultures) and roller-tube cultures. The new trick was to carry them on much longer, changing the fluids bathing the cells every two or three days, but making subcultures only after 16 to 25 days.

Three things make this propagation of virus in tissue culture of real importance. First, the myth of the strict neurotropism of poliomyelitis virus is now exploded. Many things, however, still need explaining. Why, for instance, will the virus grow in tissue cultures of adult monkey testis but not in the testis within a living monkey? Secondly, cells failed to migrate from infected roller-tube cultures as they

did from control ones. One could thus, by observing the presence or absence of outgrowth, use the cultures themselves to titrate virus, to titrate neutralizing antibody, and to type a virus serologically. Further, primary isolations of virus from human stool filtrates could be made in the cultures. As Dr. Paul said in his summing-up at the end of the Congress, "Maybe the monkey-era of poliomyelitis research is at an end." Thirdly, the culture-propagated virus of the mouse-pathogenic Lansing strain was found to lose its pathogenicity on passage while retaining some immunizing power. The possibility of developing an attenuated immunizing virus is thus no longer in the realm of fantasy.

New Virus Antigen

A second important advance was reported by Dr. J. CASALS (New York), who had obtained an antigen giving good and specific complement fixation. This has been hitherto lacking simply because of inability to obtain a reacting virus-antigen in sufficient quantity. As a rule, polio strains of the Lansing type grow (unlike Coxsackie viruses) better in grown mice than in baby ones. Casals had, however, trained a virus to grow especially well in baby mice and thus obtained virus-antigen of high titre—high enough, in fact, to react well in the complement-fixation test. The possibilities of this for diagnostic purposes had not yet been far explored, but it seemed that it was not specific for the Lansing strain of virus but gave some cross-reactions with the other two types. Here was another indication of a hope of a break-away from the need for endless monkeys.

Meanwhile, Dr. J. SALK was reporting, on behalf of a large group of U.S. workers, the results of strain typing by means of immunological tests in monkeys—the only available methods pending development of newer techniques. Active immunity tests and serum neutralizations were used and gave concordant results. Amongst 100 viruses, Type 1 (Brunhilde) was far the commonest, furnishing 85 strains; 12 were Type 2 (Lansing); and only three Type 3 (Leon). There was no evidence suggesting regular change from one type to another, from place to place, or from year to year. It is of interest, however, that of 11 strains isolated by Enders and his co-workers in 1950 by the tissue-culture technique, no fewer than 10 were of the supposedly rare Type 3 (Leon).

Dr. HOWE, of Baltimore, reported observations on the relation between antibody titre and resistance to infection in monkeys, chimpanzees, and man. He showed that the antibody-level which in chimpanzees corresponded to resistance to oral infection was roughly equivalent to that of pooled normal human gamma-globulin. Such human globulins were active against all three types; sera from Africans from the remote Ruwenzori mountains, where poliomyelitis is unknown, were as active as any. As appeared later, antibody, at least to the Lansing strain, appears much earlier in less sanitary communities where opportunities for virus ingestion are lavish.

Source of Infection

Dr. GEAR, of Johannesburg, discussed extra-human sources of poliomyelitis virus. While he could point to the presence of large quantities of virus in sewage, on flies, and even in drinking-water, he admitted that epidemiological evidence did not seem to implicate any of these as major factors in spread. The converse of this picture was described by Dr. T. FRANCIS (Ann Arbor, Michigan). Search for virus in epidemics in more sanitary communities showed that it was present to greatest degree in stools of intimate family contacts, less so in extra-familial contacts, and still less as one got further from the infected unit. Dr. BRADLEY (London), in discussion, welcomed this news as fitting in with recent epidemiological findings in Britain.

Factors Affecting Attack

There was consideration also of factors affecting the incidence and severity of attack. Dr. RITCHIE RUSSELL (Oxford) reviewed the more recent work on relations between exercise after onset of symptoms and severity of the disease. Dr. BRADFORD HILL (London) described the present position of inoculation against diphtheria and whooping-cough and the onset or localization of paralysis due to poliomyelitis. While there was nothing very new to report in these two fields, there was no attempt to deny that exercise after onset of suspicious symptoms was definitely harmful, and that insistence on absolute rest was a major contribution which the doctor could make. Equally, there was general acceptance of the association, at some times and in some places, between inoculations of various sorts and localization of attack by poliomyelitis, and appreciation of the wisdom of avoiding such inoculations at times of poliomyelitis prevalence. It was, however, emphasized that this problem was a small one compared with the very big ones of poliomyelitis, diphtheria, and whooping-cough as a whole.

Fellow Travellers

There were two important papers on the Coxsackie viruses by Dr. G. DALLDORF (Albany, N.Y.), who, along with Dr. Sickles, discovered them, and by Dr. CURNEN (New Haven). This group of viruses, named after a Hudson River town, has in the last three years caused much heart-searching about the diagnosis of abortive poliomyelitis and some other aspects of the disease. Coxsackie viruses can be recovered from human faeces and will infect suckling mice, causing paralysis possibly due to lesions of muscle rather than of brain and cord. Their point of attack varies, however, for some strains go also for brain, fat, pancreas, or liver. Their seasonal prevalence is like that of poliomyelitis virus, and in 29 instances they have been recovered from faeces along with poliomyelitis: hence several speakers referred to them as fellow travellers. They also resemble poliomyelitis virus in size and physical properties. They are of diverse serological types—at least 13, placed in two broader groups, A and B. Unfortunately, the different interested laboratories do not appear to have got together to co-ordinate the naming of the various types. There is evidence, lacking in the case of poliomyelitis, of prevalence of different types at diverse times and places. In any case they seem to be turning up all over the world. What diseases the Coxsackie viruses may cause is a matter not yet clear. Almost certainly they give rise to epidemic pleurodynia or Bornholm disease, probably also to a form of sore throat (herpangina). A relationship to serous meningitis is less certain. There was naturally great interest in their association with poliomyelitis. A very large number had been recovered from supposed poliomyelitis cases. It seemed probable that they might cause many illnesses labelled abortive poliomyelitis; but there was doubt about whether, by an interference effect, their presence might make the poliomyelitis milder or, by some other mechanism, exacerbate it.

Speaking at Harrogate on September 6, Mr. Hugh Dalton, Minister of Local Government and Planning, said that in 1925 there were 16 crematoria in Great Britain; in 1935 there were 29, in 1945 there were 58, and still only 58 in 1950, though extensions to six existing crematoria had been authorized in 1949–50—at Stalybridge, Hartlepool, Middleton (Lancashire), Northallerton, Oldham, and Skipton. In 1950 he authorized the building of six new crematoria: at Kingston-on-Thames (the foundation stone was laid by the mayor last December), Blackburn, Grimsby, Southend, Bolton, and Sunderland. This year he had chosen four other centres for new crematoria: in South-west Middlesex, Halifax, Wolverhampton, and Porchester, near Portsmouth, and had agreed to extensions of crematoria at Camberwell and Manchester. All these had been chosen so as to spread the facilities for cremation as widely as possible over the country in relation to the demand. All the new crematoria authorized since the war were municipal. Of the present total of 58 in England, Scotland, and Wales, 37 were municipal and 21 privately owned.

CONGRESS OF ANAESTHETISTS

FURTHER SCIENTIFIC SESSIONS

On the last two days of the Scientific Sessions of the Congress of Anaesthetists, held in the Old Library and Great Hall of B.M.A. House, spinal analgesia, hypotension during anaesthesia, and anaesthesia in war were among the topics discussed.

At the session held under the chairmanship of Dr. H. W. FEATHERSTONE, Dr. H. R. GRIFFITH, of Montreal, read a paper on safety factors in spinal analgesia. After stating that no anaesthetic method could be completely without danger, he listed the factors which he thought made spinal analgesia as safe as possible. He placed aseptic technique first, emphasizing that sufficient time should be allowed to ensure skin sterilization whatever antiseptic was used, and that all the equipment for giving spinal analgesia should be autoclaved together. Fine sharp needles prevented undue injury to the meninges, and the smallest effective amount of solution should be injected. He emphasized that there was a wide variation in individual tolerance to spinal analgesics, and it was better to give too little than too much. Dilute solutions should be given, as they were less irritating than concentrated ones. He felt that a combination of drugs was an advantage, and he frequently combined spinal analgesia with light general anaesthesia. Vasopressor drugs should be used only in accordance with individual requirements and never as routine practice. He pointed out the importance of prompt oxygenation in a patient who collapses under spinal analgesia; it was an invariable rule in his own department that no spinal analgesic should be administered unless there was an oxygen apparatus with masks and endotracheal tubes at an arm's length from the anaesthetist. His last two safety factors in spinal analgesia required no enlargement: they were common sense and vigilance.

Dr. E. B. TOUHY, of Washington, D.C., spoke on the adaptations of continuous spinal analgesia. He had used this method in the diagnosis and treatment of vascular or neurovascular disorders, including arterial emboli and thrombosis, diabetic gangrene, immersion foot, acrocyanosis, and thrombophlebitis. During the war he treated over 3,000 such disorders with continuous subarachnoid, epidural, and paravertebral block, and he found the subarachnoid and epidural techniques more effective and simpler to perform than repeated lumbar sympathetic block. He mentioned the value of spinal analgesia for reducing the blood pressure in hypertension and in eclampsia. He had also used continuous spinal analgesia for denervating the adrenals in patients with a phaeochromocytoma. After pointing out the beneficial effects of spinal analgesia in producing splanchnic block on patients with visceral disease such as acute pancreatitis, he quoted the work of Professor F. H. Shaw, of Melbourne, who had observed experimentally that a subarachnoid injection of a barbiturate solution caused spinal analgesia. He had verified this work and found that some barbiturates when injected intrathecally produced typical sensory and motor anaesthesia as well as a narcotic effect. Major F. MARSH, U.S.A.F., spoke of the usefulness of continuous spinal and epidural analgesia in treating frozen feet during the last winter in Korea.

Dr. P. C. LUND, of Johnstown, Pennsylvania, described the role of the anaesthetist in the management of eclampsia. He thought that the anaesthetist, who was in most cases a clinical investigator rather than a laboratory research scientist, was well suited to study and investigate this condition in co-operation with the obstetrician. The anaesthetist was trained to manage the various forms of conduction analgesia which form a large part of the modern management of these cases. The anaesthetist was, moreover, well qualified to manage the comatose patient, had a thorough knowledge of the pharmacology of sedative drugs, and could give the anaesthetic for the actual delivery.

Fits in Eclampsia

Professor R. R. MACINTOSH, of Oxford, put forward an explanation of the significance of fits in eclampsia. He said that fits were an essential feature of the condition and that to speak of eclampsia without convulsions was as meaningless as saying a patient suffered from pyrexia without a high temperature. Only 0.5% of the population suffered from epileptic attacks, but 12% of normal people displayed a cerebral dysrhythmia on the electroencephalogram. He had investigated with the E.E.G. the 33 patients who had been admitted to the Radcliffe Infirmary during the past four years with eclampsia. Of the first six examined in a preliminary investigation five had a cerebral dysrhythmia; he then wrote to all the remaining patients to inquire if there was a family history of fits, and, of 21 replies, one-third admitted such a history—but this figure was probably low because of the patients' reluctance to give the information. Whether a person had convulsions or not depended on the severity of the outside stimulus—anoxia, the toxins of pregnancy, or any other agent—and the stability of his cortical discharges; those with an unstable rhythm would have convulsions in response to a lower stimulus than others. Known epileptics were not likely to develop fits due to toxaemia of pregnancy or the so-called "anaesthetic convulsions," as they were almost invariably under heavy sedation. He went on to outline treatment by the anaesthetist of a patient having an eclamptic fit. During the tonic stage any attempts at artificial respiration were useless, but during the clonic stage oxygen should be given. The anaesthetist should aim at stopping the convulsions as soon as possible and preventing their recurrence, and there was no doubt that the injection of 0.25 g. of thiopentone was a practical and effective emergency measure.

Static Electricity

The last day of the Congress was opened with a paper from Dr. T. GORDH, of Stockholm, on the prevention of static electricity in anaesthetic apparatus by radioactivity. Professor R. R. MACINTOSH was in the chair. Dr. Gordh said that earlier in the year an anaesthetic explosion due to static electricity had occurred in a hospital in Stockholm, when a mixture of nitrous oxide, oxygen, and ether exploded in the rebreathing-bag of a semi-open machine. He described experiments which were made at the Radiophysical Institution at the Karolinska Institute in Stockholm. Filling a 5-litre dry rebreathing-bag with oxygen generated electric potential to a voltage of 250, and breathing into the apparatus gave a potential of 300 volts; if the bag was previously stroked with a woollen object, up to 2,000 volts was obtained. But if a radon tube of 50 mg. was placed at a distance of 50 cm. away, charging of the bag was impossible. On the strength of this and other experiments it was concluded that radioactive substances prevented the formation of static electricity. Dr. Gordh emphasized that his investigation was a preliminary one, but hoped it would open the minds of anaesthetists to the new possibility of preventing static electricity in anaesthetic apparatus.

Later in the morning Dr. R. W. COPE, of University College Hospital, spoke on anaesthesia in war. He described his work in a mobile surgical team in the Middle East during the last war, and said that in the four teams which travelled from Egypt to Benghazi and then back to Tobruk 672 operations were performed under thiopentone alone. Dr. Cope illustrated with a case history the ease with which an overdose of thiopentone could be administered under Service conditions. In battle the anaesthetist was responsible for inducing the patient quickly so that the surgeons should not have to wait between their cases; moreover, the induction should be complete before the outer bandages and the patient's clothes were removed. The surgeon should not be limited in his time of operating by considerations forced on him by the anaesthetic, and easy maintenance of anaesthesia was important, so that two tables might be kept in operation by one anaesthetist if necessary. He had

administered ether by means of a baby-food tin with two nail holes knocked in the lid, but as the campaign advanced surgical units were issued with the Oxford vaporizer, which he described as "the most valuable piece of equipment ever received." Cyclopropane was brought into use only at the end of the war, and he thought it of great value for surgery in the forward areas. He pointed out that in the event of future war natural curare would be scarce, and synthetic relaxants should therefore be further developed. Strong and simple anaesthetic apparatus was necessary, and the present designs for civilian use would have no place in battle. He concluded by saying that in any conflict it must never be forgotten that any patient who reached a surgical team, whether he was friend or enemy, was deserving of the highest degree of kindly efficiency.

Methonium Compounds

The afternoon session, under the chairmanship of Dr. W. A. Low, of St. Thomas's Hospital, was mainly concerned with hypotension under anaesthesia. Dr. G. E. H. ENDERBY, of the Plastic Jaw Unit, Basingstoke, spoke of the use of the methonium compounds and postural ischaemia. It was possible to reduce the blood pressure with these drugs, the degree varying widely from patient to patient, but to obtain adequate hypotension it was often necessary to make use of other factors, such as tilting the body so that the blood drained into the legs, and controlling or assisting respiration to increase the interpulmonary pressure. He described his technique with hexamethonium iodide, which he had used in about 300 cases, of which the first 50 were experimental. Of the remaining 250 a satisfactory operating site was obtained in 58%, in 35% bleeding was reduced, and in only 7% was it impossible to obtain adequate hypotension. He thought it wise to limit the procedure to patients who were relatively fit and healthy, and to exclude those who showed signs of insufficiency of the coronary arteries.

Dr. G. S. ORGANE, of the Westminster Hospital, recalled that one could still produce ischaemia of the limbs with tourniquets, and in the superficial tissues with injections of adrenaline solutions. But there were operations in which the anaesthetist was justified in undertaking some risk to ensure reduction of bleeding. This could be obtained by reducing the blood pressure with chloroform, thiopentone, the methonium compounds, spinal or epidural block, and by exsanguination. He thought it was unjustifiable to use chloroform, and if thiopentone was given to keep the blood pressure low during a lengthy operation it produced a long period of unconsciousness afterwards. The methonium compounds allowed the anaesthetist to control the hypotension independently of the depth of anaesthesia. He found that the younger patients required larger doses and provided the highest number of failures, and that the reduction in blood pressure was most reliable in middle-aged patients with moderate hypertension. He felt that the first dose must be the effective one; it had been noticed by physicians administering oral hexamethonium that tolerance was rapidly built up to a succession of inadequate doses. He referred to the method of exsanguination and interarterial transfusions, and pointed out the danger of haemodilution when large volumes of blood were removed from the body. The technique of controlling hypotension was effective, but cases must be selected carefully and the anaesthetist must be constantly attentive to the condition of the patient.

A report from Washington announces that two new kinds of protective clothing made of plastic substances and nylon are soon to be tried out by stretcher-bearers of the American army in Korea (*Le Figaro*, September 11). The new "armour," varying in weight from two to eight kilograms, is designed to protect the troops from shrapnel and stray bullets, and can offer only slight protection against close-up rifle or machine-gun fire. A new type of helmet is also to be tried out; this is made of aluminium and lined with laminated nylon.

Nova et Vetera

JOHN KIDD (1775-1851)

It is given to few to achieve success in more than one branch of knowledge, and to fewer still to hold a number of official positions simultaneously and with distinction. John Kidd, who died a century ago on September 17, 1851, was a remarkably versatile man. He studied medicine at Guy's Hospital, and after graduating M.B. was appointed chemical reader at the University of Oxford in 1801, the first Aldrichian professor of chemistry in 1803, and Lee's reader in anatomy in 1816. At the same time he was physician to the Radcliffe Infirmary and had a busy private practice. He resigned the Aldrichian professorship in 1822, when through the influence of his former teacher and lifelong friend, Sir Astley Cooper, he was elected regius professor of physic in the University.

A keen geologist, he published *The Outlines of Mineralogy* in 1809, while his interest in chemistry is reflected in his "Essay on the Spontaneous Production of Salt-Petre," which appeared in the *Philosophical Transactions* for 1815. His Bridgewater treatise *On the Adaptation of External Nature to the Physical Condition of Man* (1833) was reputedly the most popular of the series, reaching a sixth edition in 1852. In 1834 Kidd was made keeper of the Radcliffe Library, supervising the cataloguing of its books on medicine and natural history. His versatility also extended into the field of Greek scholarship.

A small man who stalked through the streets clad in a spencer, he is said to have been the first Oxford physician to discard the traditional trappings of his profession—the wig, the large-brimmed hat, and the gold-headed cane.

An outline of what W.H.O. stands for was given by Sir Andrew Davidson in a speech at Paisley Rotary Club recently. He said that there were now about 75 States in membership. The last three to be admitted—at the fourth World Health Assembly last May—were Japan, Germany, and Spain. The increased speed of transport meant that epidemic diseases anywhere in the world were of universal and not merely local concern. It was for this reason that the International Sanitary Regulations, approved in May, 1951, were of such importance to all nations. The trend of world population was also a matter to be examined carefully. Since the beginning of this century the world population had increased by 825 million persons (53%); it was now about 2,377 millions, compared with 1,551 millions in 1900. Increases in population of these dimensions brought problems of proportional magnitude and complexity—housing, food and nutrition, infectious diseases, maternity and infant health, industrial health, education of medical and other health workers, and so on. The health organizations of different nations varied widely both in standards and in problems. In most countries, mainly the poorer ones, there was a severe shortage of trained workers. Finally, there was nowadays a growing appreciation that weakened resistance, poverty, malnutrition, and bad social environment facilitate the spread of disease. All these four trends, apart from others of a political nature, helped us to realize that our interest in world health was as much concerned with self-protection as with altruism. By demonstration teams, by travelling fellowships, and by providing specialist advice on strengthening health services in backward countries W.H.O. had helped to improve their knowledge and achievements. W.H.O. was also helping in the control of malaria in many parts of the world, and, combined with Unicef and the Scandinavian Red Cross Societies, was playing a valuable part in the campaigns against tuberculosis and venereal diseases.

Correspondence

Ethics and Psychiatry

SIR,—The two controversies, concerned respectively with the ethics of leucotomy and the mechanism of conversion, which have recently been running a parallel course in the *Journal* have released an impressive amount of moral indignation. Readers are moved to protest at the violation of the traditional concept of the relationship between doctor and patient implicit in certain approaches to treatment, and to proclaim the right of the individual to decide what shall be done to his own body or mind. For this at least we can be thankful.

But whence comes our profession's concern either with ethics or with the value of the individual? What in fact is the source of that moral sense which many of us take so much for granted? Morality does not lack a fundamental basis: but where else can that basis be found but in the religious background to human thought and feeling—in the idea of God Himself?

It is surely the failure to meet this issue squarely that is responsible for so much of the confusion evident throughout the course of these controversies. The Freudians deplore the mutilations of the leucotomists, while the experts in physical treatment attack the dialectical rigidity of psychoanalysis: but both schools in fact share a mechanistic and determinist philosophy and borrow their moral standards from a religion whose central creed they ignore.

The idea that the individual has a unique value rests, as Rex Warner has pointed out (*The Cult of Power*, 1946, p. 140), "on a belief in a God for whom every soul is valuable. . . ." Moreover, the idea of man's spiritual work derives ultimately from a belief that he has a soul which is created in God's image and links him to God unless he denies or rejects that union. If we lose or ignore these beliefs we cannot expect indefinitely to preserve the morality founded upon them. We have only to look around us to see the direction in which failure to appreciate this fact is leading mankind.

One may regard both physical methods of treatment and psycho-analysis as potentially valuable techniques, without either subscribing to the materialist philosophy of Freud or accepting Dr. Sargant's mechanistic explanations as the ultimate truth about man. But in the long run we cannot maintain an ethical basis for our professional decisions about treatment, or indeed for our lives at all, if we refuse to recognize that the sole source and origin of morality is ultimately religious.—I am, etc.,

London, S.E.1. DAVID STAFFORD-CLARK.

Poor Results with Dihydrostreptomycin

SIR,—Since our introduction of streptokinase as an adjuvant to streptomycin in the treatment of tuberculous meningitis, until the beginning of 1950 we used streptomycin sulphate both intrathecally and intramuscularly. This choice was merely because the salt mixed with streptokinase without precipitate formation, and for no other reason. At the beginning of 1950 our stock of the sulphate was exhausted, and as dihydrostreptomycin sulphate mixed harmlessly with streptokinase and was readily available we turned over to this.

With the introduction of streptokinase we standardized our intrathecal streptomycin administration in six-week courses, and this regime has been continued up to the present. For purposes of comparison we have a series of 40 cases which received intramuscular and intrathecal streptomycin sulphate, and 14 admitted during 1950 which received dihydrostreptomycin sulphate intrathecally. Seven of these 14 had the streptomycin calcium chloride complex intramuscularly and seven had dihydrostreptomycin sulphate intramuscularly.

Late in 1950 it became apparent that our results were much poorer than those obtained earlier, and the results could not be correlated with the stage of the disease or resistance of the organism to streptomycin. We therefore reviewed our treatment, and the main difference between the two sets of cases appeared to be that the first had had streptomycin sulphate and the second dihydrostreptomycin sulphate. Of the 40 treated with streptomycin sulphate 23 (later reduced to 22) survived. Of the 14 treated subsequently three have survived. Of the 22 surviving patients treated with streptomycin sulphate none is deaf. Of the three survivors treated with dihydrostreptomycin sulphate two are deaf. These three survivors were all treated by dihydrostreptomycin by both routes. Further, one child treated only intramuscularly with dihydrostreptomycin (for tuberculous peritonitis) is also deaf.

The numbers from one centre are, of course, small, and we are accustomed to bad runs of cases. Yet we are perturbed by our poorer results and the increase in deafness since dihydrostreptomycin was introduced. It is unfortunate how seldom are precise details of the streptomycin preparations used included in the reported series, and this hospital has been no exception in this respect. Quite fortuitously we are able to pinpoint the time at which the change from streptomycin to dihydrostreptomycin sulphate was made, and our results incline us to retrace our steps.

In spite of the claims of lesser neurotoxicity made for dihydrostreptomycin, the risk of deafness cannot but be worrying. We did not expect, however, that concomitantly our results would deteriorate, and we would be interested to learn if other centres have had similar experiences.—We are, etc.,

The Hospital for Sick Children, Great Ormond Street, W.C.1. I. A. B. CATHIE. D. H. GARROW.

South Bank Manners

SIR,—I write to make clear that neither I nor any officer employed by the Lambeth Borough Council is in any way responsible for the conditions described in your annotation (September 8, p. 596). The Festival of Britain Ministry arranged everything. Not until the volume of complaints raised the issue was entry to the South Bank by June 19 extended to the staff of the public health department. The Exhibition was then in full swing and of course only minor improvements were possible. The managements of the catering establishments there have worked hard under such adverse conditions to feed the public that your condemnation of them is unfair.

The Festival Gardens on the other hand have worked from the beginning in close alliance with the staff of the Battersea Borough Council not only in planning the kitchens, stores, staff amenities, and other behind-the-scene premises, but also in the day-to-day running. No complaints of any substance regarding the standard of catering in the Gardens have been received in consequence.—I am, etc.,

A. G. G. THOMPSON,
Medical Officer of Health,
Lambeth and Battersea.

Examination of Male in Nullity Suit

SIR,—It may be that the practice and requirements of the High Court, Probate, Divorce and Admiralty Division (Divorce) varies in different registries. I imagine this possibility to be remote, since I have examined, in Manchester, both petitioners and respondents whose causes were filed in London.

If I am correct in my surmise, the answer given ("Any Questions?" September 1, p. 557) is out of date and misleading. It is no longer the practice to appoint two examiners. One is now usual, and the examination ordinarily takes place at his consulting-rooms.

The questioner does not say if he is the appointed examiner or the independent witness in a contested suit.

If he is the former, his findings should be given in a standard form. He will probably find the High Court registrar ready and willing to set out an imaginary report, couched in the archaic but unambiguous language to which the legal profession still adheres. Objectivity is essential and the answers of the examined person are valueless. If he is an independent witness in a contested suit he may bring any evidence he wishes. He would be wise to bear in mind, however, that it may have to withstand cross-examination.—I am, etc.,

WALTER CALVERT,
Medical Inspector in Matrimonial Causes, Probate, Divorce and Admiralty (Divorce) Division.
Manchester District Registry.

SIR,—As the answer ("Any Questions," September 1, p. 557) does not give an entirely accurate presentation of the facts I feel I should make some comments. Since July, 1948, as a result of the Denning report, only one medical inspector is appointed to examine and report in undefended cases, and, if the Registrar so decides, in defended cases too. This personally I regard as a retrograde step, as until a case comes up for medical examination no one can say whether the findings will be easy or difficult to interpret. And it is of great assistance to be able to discuss difficult cases with an experienced colleague. The Registry can be asked to appoint a second inspector if in any special case the examiner regards it as necessary.

However instructive it would be to carry out a full psychological investigation of each case, a prolonged interrogation is not usually looked upon with favour by the Court. In fact some judges seem to prefer that no questions should be put to the parties at the medical examination, and neither party is of course obliged to give any answers to the official medical examiner. The form of the medical report has now become almost completely standardized. If there is any physical impediment to consummation that would be stated, but if there is no physical impediment the man is reported as being "*apparently* capable of performing the act of generation." A medical inspector is invariably called to the witness box to prove his report, and it is then that he may be questioned by counsel or judge as to indications of psychological impotence. The examiner, who will have been in Court during the hearing, will have had the opportunity of listening to the full history of marital relations between the parties. This plus other evidence given and the examiner's own estimate of the husband's make-up is usually sufficient for the guidance of the Court.—I am, etc.,

H. C. SQUIRES.
London, W.1.

Proper Scheme of Notification

SIR,—The reply to the question about the isolation and notification of scarlet fever ("Any Questions?" September 8, p. 621) no doubt had to be brief. Much more could be said if space permitted. The logical step is, of course, to make tonsillitis notifiable, but notification would probably be very incomplete. On the other hand, who dares to discontinue any measure of control involving an organism with the potentialities revealed in the Brighton and Hove outbreak of sore throat in 1929? About five weeks elapsed between the first case and the recognition that milk was the vehicle (H. H. Scott, *Some Notable Epidemics*, p. 195. Arnold, 1934; and *Annual Report of the C.M.O. of the Ministry of Health for 1930*, p. 59). More than a thousand families were affected, with 65 deaths. Had the presence of a rash led to notification the outbreak would probably have been cut short. There is room for a scheme of notification in which the practitioner has an obligation to notify any important disease which he believes to be occurring in epidemic form, regardless of the prescribed list and without the inhibiting thought that the notification may be used only for statistics.—I am, etc.,

W. B. WATSON.
Bingham, Notts.

Resistance of the Body to Cancer

SIR,—The following very ordinary cases, among many others, were observed by me:

Case 1.—Woman, aged 65, died of exhaustion and wasting: she had multiple secondary cancerous growths in bones, glands, lungs, and skin. Left breast removed for cancer 12 years before; there were no signs or symptoms of recurrence for 10½ years. Three years before her death she had vague pains referred to the right loin; her chest and abdomen were radiographed then and nothing abnormal was found.

Case 2.—Woman aged 60; left breast removed for cancer 11½ years before. Her relations and friends assured me that she had been well and strong until six months before I saw her. I found that she had quickly growing cancers in lungs and ribs. In both these cases the malignant nature of the original growths had been proved by pathologists.

Case 3.—Thirty-six years ago a woman had extensive cancer of the cervix; the growth was fixed by infiltration of the surrounding tissues. In consultation with another surgeon we agreed that it was inoperable. But I sent her to the late Dr. Eden. He said it was hopeless to think of a cure, but to relieve her he did Wertheim's operation. She is now 96 and very well.

Case 4.—A patient had advanced cancer of the cervix. I performed a panhysterectomy with removal of glands, but said that the operation would be unsuccessful, as some of the outlying growths could not be removed. Soon afterwards Mr. Ian Robertson gave her radium treatment. For many years she had very good health and examinations revealed no signs of cancer. Eventually, after 10 years, a lump of growth formed in the pelvis and extended rapidly; she died 11 years after her operation.

In Cases 1, 2, and 4 it is not likely that the cancer cells were of low virulence, as in the second attacks they showed great activity in multiplying and disseminating themselves. During the 10 years that they were not apparently growing they were there and potentially active, but were inhibited; some anticancerous influence appears to have been at work.

Years ago, and sometimes even now, a five-year period of freedom from recurrence has been hailed as a success by surgeons. This is obviously wrong—13 or 14 years must elapse before the trouble can be considered to be eradicated. But the patient need not be worried all this time—she is getting a fair slice of life.

This long latent period in the activity of cancer cells after an operation on the breast needs research and thoughtful consideration. Evidently the resistance of the body can keep these cells quiet for many years. It may be that a balance of sex, pituitary, adrenal, and other hormones helps this resistance. The advent of cortisone has generated new and far-reaching ideas about the reaction of the body, with its hormones, to some diseases. Some change in the hormonal content or in the chemistry of protein metabolism in the body could remove these inhibitory influences and then the cancer cells break out, disseminate, and grow with all their horrible activity. Very, very rarely an inoperable cancerous growth in the human body has been found at a subsequent operation to have disappeared, apparently entirely. The effect of stilboestrol on cancer of the prostate is of great significance; it can be explained only on the hypothesis that the sex hormones are of much importance in influencing cancer.

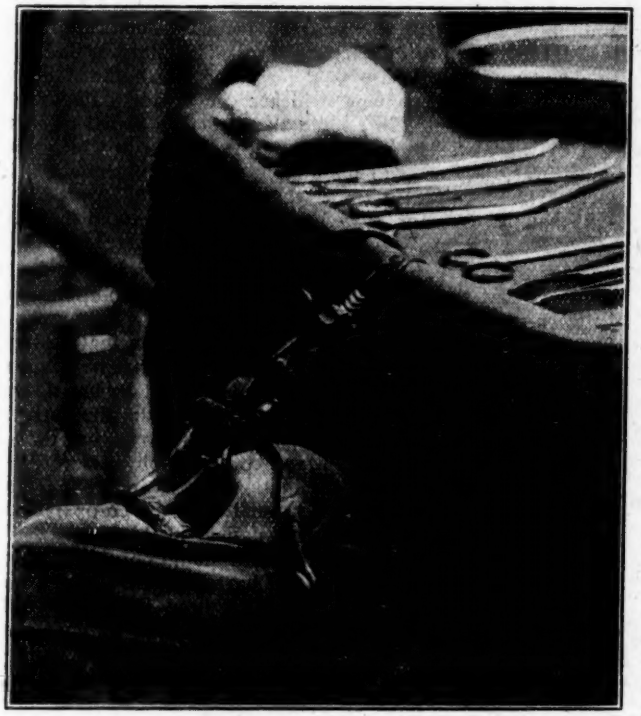
The resistance of the body and its reparative efforts against all noxious influences, such as injuries, infections, loss of blood or tissue fluids, secretory defects or hormonal failures, is the most prominent thing in pathology; on it our lives chiefly depend. It is probable that there is some resistance to cancer cells and their poisons, though this is usually only effectual or partially so when there is a small amount of malignant tissue to be attacked. Resistance to a "new" cancer is shown in cases of the atrophic type of growth in the breast, which can survive for over 20 years without any treatment.

What is happening to the cancer cells during the eight or ten years in a woman who keeps well for that time after her operation, only to succumb later?—I am, etc.,

HARRY GABB.
Hastings.

Suspension of Gag for Tonsillectomy

SIR,—Various ingenious and on the whole complex methods appear in print from time to time for holding up the free end of the Boyle–Davis gag during tonsil operations. Cord suspension attached to a pulley in the ceiling, harness pressing on the chest, specially designed props on the hand of the anaesthetist, have all been used. The method illustrated is not universally known. It has the merit of



simplicity, it is effective, and only requires an adjustable instrument table possessed by nearly every hospital. An additional advantage is that the instruments, swabs, etc., may be placed on the table in the direct line of vision of the surgeon, and not on a side table.—I am, etc.,

Doncaster. PHILIP H. BEALES.

Treatment of Plantar Warts

SIR,—I read with much interest the article by Drs. D. A. Duthie and D. I. McCallum on the treatment of plantar warts with "elastoplast" and podophyllin (July 28, p. 216), but I was very much surprised to see that the time given for a cure was six to eight weeks, and then in only 60% of the cases.

I have used CO_2 snow for over 40 years for the treatment of plantar and other warts and I have found it most efficient, and as I was medical officer to three schools I had plenty of opportunities, especially when one of the girls' schools got an epidemic of verrucas. The treatment is simple: pare the wart as much as possible without making it bleed, then apply the pencil of snow for about two minutes (rather longer in adults and shorter in children under 14), put a little mild antiseptic powder on (not boracic), wait for 10 or 14 days, and repeat the process—but if the wart still shows distinct roots and not much dead skin give it two and a half to three minutes; I have in adults given four and a half minutes. These two treatments will cure quite 50% of the warts, but often a third treatment is necessary. These three treatments cure at least 90% or 95% of the cases.

In some adults with old verrucas that have been treated with acids, operations, etc., for some years I have had to give four or five treatments, but in all those 40 years I have never failed to cure a verruca, and the vast majority have been cured in two or three weeks. The podophyllin and elastoplast treatment is of some use in multiple warts. Radium, of course, is good, but is a great trouble and expense, and if one can cure a wart at home with CO_2 snow, why use radium?

The use of CO_2 snow seems to have gone out of fashion, but with it the colour of moles can be removed and made white with no scar, though it does not remove the hairs. Naevi, especially in young children, can be most successfully removed, and all that remains is a slight colourless scar, but in a baby the snow at the first application must not be kept on more than 10 seconds, for some are very sensitive, but the results are excellent.—I am, etc.,

Limpsfield, Surrey. G. D. LAING.

Throat Packs

SIR,—For three years we have used for packing throats in surgery of the mouth and nose a proprietary vaginal tampon. This seemed a logical procedure, since the purpose for which this was designed is closely analogous. The advantages we find are the following: less post-operative sore throat; good absorption of blood, etc.; good occlusion of the hypopharynx with no leak past the pack; easy insertion; the pack is small and therefore causes little forward bulging of the tongue. This is often a great advantage to the dental surgeon. For each patient we use two packs, one on each side of the endotracheal tube. There is no need to moisten or lubricate them before insertion and they can be secured by a haemostat fastened to their strings. This obviates the risk of the pack being left in by oversight after the tube is withdrawn.—We are, etc.,

St. Thomas's Hospital, S.E.1. J. G. BOURNE. J. H. HOVELL.

Herpes Zoster Treated with Antihistaminics

SIR,—Two early moderately severe cases of herpes zoster of the right side, one involving the nipple area, both well vesiculated, and in males between 60 and 70 years of age, were treated with promethazine hydrochloride 5 mg. orally three times a day for six days, and by the local application three times a day for the same period of a lotion containing calamine 8% and diphenhydramine hydrochloride 1%.

Both patients when seen on the eighth day after beginning treatment showed almost complete desiccation of the vesicles with some of the "crusts" separating from the skin. Each asserted that he was free from pain and discomfort. A further examination six days later and seven days after the cessation of treatment showed further separation of the dried lesions, while each patient seen separately said he had again remained free from pain.

It does appear that in these two cases the usual course of the eruption was shortened, the pain was relieved without analgesics, and no post-herpetic pain was experienced.—I am, etc.,

Polegate, Sussex. J. M. MORAN.

Retropubic Prostatectomy

SIR,—Mr. Eric Coldrey in his modification of the Millin retropubic prostatectomy (September 1, p. 530) has re-emphasized that the retropubic transvesical operation, as described by Millin on p. 138 of *Retropubic Urinary Surgery* (1947), is a possible operation for those who are unable to master the retropubic technique. The retropubic transvesical operation has been done accidentally on numerous occasions when the operator fails to recognize the vesico-prostatic junction (which can be so readily identified by palpation, and sometimes by the presence of a transverse vein) and makes the supposed incision in the capsule too high.

There are three main criticisms of this modification. First, difficulty in obtaining a neat plane of cleavage between capsule and adenoma. Secondly, after enucleation of the main adenomatous mass it is difficult to visualize clearly the apex of the prostatic cavity in order to detect small residual

adenomata. Thirdly, the urethra must be torn with the finger instead of being cut with scissors—thus increasing the risk of incontinence, temporary or permanent.

In our experience where the retropubic transvesical operation has been performed accidentally there has rarely been any serious complication, and no case of bladder-neck stenosis or residual adenoma has been encountered. We would suggest that anybody capable of performing the retropubic transvesical operation could equally well perform a classical retropubic—but for the occasional prostatectomist the Freyer with bladder closure will still have the lowest mortality if not morbidity.—We are, etc.,

London, S.W.7. G. M. LEWIS.
D. M. WALLACE.

SIR,—The memorandum by Mr. E. Coldrey (September 1, p. 530) on prostatectomy seems to demand comment.

1. The transverse incision in the bladder wall must cause more haemorrhage and there seems little advantage in enucleating the prostate.

2. The Harris technique gives good light to clear up the prostatic cavity and control haemorrhage, and the boomerang stitches in the bladder base reduce the cavity and prevent stenosis.

3. Stitching the catheter to the foreskin or the glans seems a horrible procedure and must be painful, whereas the inner end of the Harris catheter is soundly anchored to the glass rod on the abdominal wall and thus keeps the eye or open end of the catheter where it is wanted.

4. I do only a small number of prostates, but I am sure that it must be wrong to do immediate prostatectomy in a case of acute retention. These cases show a very poor urine urea—often as low as 1—and the blood urea is high, so that even a cystostomy in these cases, in an old man, is fatal, whereas a soft rubber catheter properly tied in for two weeks brings the estimations up to normal and the general condition of the patient—tongue, appetite, etc.—is much improved.

The technique of tying in the catheter with elastoplast is very important, and few can do it. A thin layer of gauze is put round the penis behind the corona, then a layer of elastoplast 1½ in. broad; then two 0.5-in. strips vertically and round the catheter, held by a final strip round the penis on top of the first. The plaster sticks to the catheter and keeps it in, and it need not be changed for a week very often. The urethritis is of no consequence, nor is the occasional bleeding. Sulphadimidine is administered. This leaves the abdominal wall clear for operation. The De Pezzer is also a terrible instrument. This procedure is infinitely safer than prostatectomy or even cystostomy.—I am, etc.,

Chigwell. N. BEATTIE.

SIR,—Mr. Eric Coldrey (September 1, p. 530) has advanced the art of prostatectomy by returning to the transvesical route. Everyone longs for the wide open spaces—the urologist, the surgeon with an abdomen full of adhesions made by his predecessor, and even the Rugger player with the ball in the scrum. The only rational reason for descending to the retropubic route was the avoidance of suprapubic fistulae. In my "Aseptic Prostatectomy" (see *Brit. J. Surg.*, 1945, **33**, 41), with three rows of sutures in the bladder wall there are not more than 1% of temporary suprapubic leakages. Two rows of sutures are insufficient. The vesical wall heals far better than the pubo-prostatic ligaments, and consequently leakage after the retropubic route is commoner. The vertical vesical incision, for anatomico-vascular reasons, heals bettter; it is also capable of being prolonged downwards into the pubo-prostatic ligaments in the radical operation for cancer.

Mr. Coldrey's article is a description of "Aseptic Prostatectomy" without the asepsis (see my "The Catheter and the Prostate," *British Medical Journal*, 1946, **2**, 757), but he does use my sodium citrate, with diathermy as the only haemostatic agent; and supports my advocacy of curing the acute retention by an immediate prostatectomy. Asepsis is still necessary, since many of our ward microbes are becoming antibiotic-resistant. My friend Mr. Terence Millin must be shocked to see the "Wilson Hey prostatectomy" described as a modification of his retropubic prostatectomy.

I regret that Mr. Coldrey prohibits the general practitioner from passing a catheter but immediately passes that lethal weapon himself.—I am, etc.,

Manchester. WILSON HEY.

The Doctor's Responsibility

SIR,—In the *Journal* of September 8 (p. 616), you published an account of a High Court action in which damages amounting to £3,550 were awarded against a doctor and the board of governors of Charing Cross Hospital for failure to diagnose broken ribs, as a result of which the patient eventually died. In giving evidence the doctor stated that the patient was intoxicated and there was no denial of this fact by witnesses—indeed, recalling the manner in which the injury was sustained, no reasonable person could doubt the fact. The doctor also stated that the patient "repeatedly said that there was nothing the matter with him and that he wanted to go home."

Now, Sir, the very first essential of diagnosis in any condition is that there must be mutual trust and co-operation between patient and doctor. If a patient says, "I have a pain in my leg," we must proceed on the assumption that he has indeed got a pain in his leg, and if he states that he has no pain in his leg, it is surely to be assumed that he has none. If the negative assertion is to be disbelieved, be the patient black or white, drunk or sober, it surely follows that every consultation must develop into a complete physical, radiological, and pathological examination. It is apparent from the evidence that this essential mutual trust and co-operation was not given by the unfortunate patient in this case.

Mr. Justice Pritchard said that if a stethoscope had been used the true condition would not have been missed. From a purely clinical standpoint the fractured clavicle would probably have been evident, but if leakage of air into the pleural cavity had not yet occurred it is difficult to understand the importance of the stethoscopic examination. Mr. Justice Pritchard added that the intoxicated state of the patient should have put the doctor more on his guard than usual. Exactly how much patience is a doctor expected to exercise when dealing with inebriates? If the doctor had said, "I forbid you to go home," and proceeded to remove the patient's shirt against his express wish, would he (the doctor) have found himself in the same court facing a charge of assault? How much tolerance would the learned judge show to an intoxicated witness in the box?

I echo Mr. Justice Pritchard's advice to the doctor—viz., that he should not be unduly depressed about the unfortunate outcome of the case. There are few of us who would not have done exactly the same in similar circumstances, although those of us with a little more experience of human nature would have obtained a statement, signed by the patient, that he was going home at his own wish against advice. If the patient either would not, on account of truculence, or could not, on account of intoxication, sign his name we should simply request such a signed statement in the presence of a witness.

I shall be interested to learn the date of the appeal against this legal decision.—I am, etc.,

Leicester. J. K. M. DEAS.

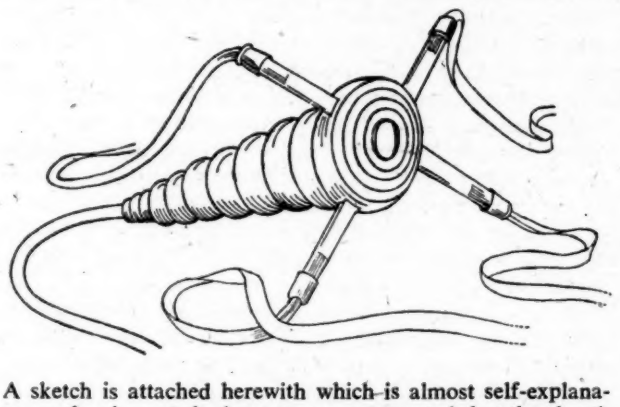
Appliance for Male Incontinence

SIR,—The incontinent male patient has always presented a difficult problem to his medical adviser. Appliances have been on the market for many years, but these have tended to be both cumbersome and expensive. Such apparatus has required constant cleaning to prevent its becoming unhygienic, with the result that it has had to be duplicated or even triplicated. A patient of this type who is confined to bed has always found great difficulty in the constant wearing of what amounted to a dead weight on a particularly sensitive organ.

In the early part of last year the writer was privileged to visit a well-known London geriatric unit. In that special clinic the ordinary rubber condom was being used as a fitted appliance and connected with a length of rubber tubing leading into a suitable receptacle. The idea was novel, cheap, and appeared to work very well. On returning to this hospital the method was brought into use, and was found to be a great saving both of nurses' time and of laundry bills; when successful, the laundry charges were reduced in some instances to 25% of their former figure.

After a month's fair trial the head male nurse pointed out that there were several improvements which could be effected. *Inter alia*, the condom itself and the tube tied on to it were liable to kink and so cause disaster. In addition, the anatomical structure of the male patients concerned varied considerably, and the condoms purchased in large numbers were unfortunately uniform. It was found impossible to attach a tape or other secure anchorage, and as a result patients were apt to pull off the rubber envelope.

At this stage contact was made with a leading manufacturer of surgical appliances, and his co-operation was secured in a series of experiments in order to produce a better drainage system. Several trial fittings were produced and returned to the maker with notes for further improvement. The final result is very satisfactory indeed and is not costly when measured in terms of financial saving and patient's comfort.



A sketch is attached herewith which is almost self-explanatory; the rings at the base are so constructed that the sheath can fit any size of male organ by means of the simple use of a pair of scissors. The rubber has been specially treated and can be boiled or washed in antiseptic with only very slight deterioration. The corrugations have made the collecting piece so that it does not kink. The drainage tube is of the same rubber, but the walls are of such a thickness that obliteration of the lumen is almost impossible. The appliance is now on the market and can be purchased from any leading supplier under the name of the "Simplic" Bed Incontinence appliance.

My thanks are due to the male nursing staff for their co-operation and the interest they have taken in the evolution of this labour-saving device.

—I am, etc.,

Leicester. JOHN A. CHAPEL.

Treatment of Blepharitis

SIR,—I should like to congratulate Mr. D. Ainslie on his excellent paper on "The Treatment of Blepharitis" (September 8, p. 582). I agree with it entirely, particularly the point that dandruff of the scalp must be simultaneously dealt with, and that errors of refraction must be corrected.

Until such time, however, as aureomycin is in more ample supply I would like to stress the value of liquor tinctorium *B.P.* in the treatment of this condition. I have used it for many years on very many cases and would almost be prepared to say that it is specific if properly applied. The crusts are removed first of all by small pledgets of cotton-wool wrung out of sodium bicarbonate lotion; the liquor is painted on the eyelid margins at night and as much as possible removed the following morning, again with pledgets of cotton-wool wrung out of the alkaline wash. Admittedly the colour is a drawback, but, except perhaps with half-grown schoolboys, enough is removed by the morning cleansing to make the treatment quite possible, and when it is pointed out to the parents that the continuation of the blepharitis frequently leads to a diminution in number, and a deterioration in quality, of the eyelashes they are usually willing to co-operate.—I am, etc.,

Royal Eye Hospital, London. A. J. CAMERON.

Rupture of the Spleen

SIR,—Dr. N. N. Iovetz-Tereshchenko's letter (September 8, p. 608) prompts me to record two such cases.

A healthy fireman aged 45 ran his motor-cycle into the back of a stationary van while trying to avoid a pedestrian who had stepped in front of him. He appeared to be only superficially injured, but was taken to hospital and was luckily admitted. At about midnight he was in a seemingly moribund condition, but after transfusion he revived I was called to see him in the morning, and found that he had considerable abdominal pain and obvious signs of free fluid in his abdomen. A laparotomy was performed and the spleen was found to be literally floating in the abdomen and ruptured in three places. After evacuation of the blood and splenectomy the patient made an uninterrupted recovery.

A man aged 70 was knocked down by a motor-cycle. Both he and the motor-cyclist concerned had sustained fractured skulls. I saw him when he was comatose and generally in a very poor condition. His general condition was so bad that no further examination was made, but the post-mortem examination revealed that he also had a ruptured spleen due to fractured ribs, and some lung laceration.

Rupture of the spleen must be uncommon in British hospitals, but these two cases seem to indicate that perhaps one should bear it in mind, after abdominal injuries, more than one usually does. Again, the latent period of freedom from symptoms is extremely deceptive.

In his letter Dr. Iovetz-Tereshchenko does not state whether any of his patients were malarious, since the malarial spleen is always supposed to be abnormally fragile, but in Case 1 there was definitely no malarial history.—I am, etc.,

Harrow. J. STEPHENS.

Charles Dennis Fisher

SIR,—I am writing a biographical sketch of Charles Dennis Fisher, brother of the Rt. Hon. H. A. L. Fisher and Admiral Sir W. W. Fisher, who lost his life in the Battle of Jutland in 1916. From October, 1914, to July, 1915, he was engaged in motor ambulance work in Belgium and Northern France, being mentioned in dispatches for conspicuous gallantry during the second battle of Ypres. I am most anxious to obtain further information about his work at that time, and would be greatly obliged if you would publish this letter in your correspondence columns, in the hope that some of your readers may be able and willing to help me in the matter.—I am, etc.,

10, Drayton Gardens, Kensington, S.W.10. CHARLES TENNYSON.

POINTS FROM LETTERS

Penalties for Sexual Offences

Dr. ELLIS STUNGO (London, W.1) writes: . . . Dr. H. Ward-Smith, with his experience of victims of homosexual assaults, may agree that some boys invite trouble and can indeed constitute sexual seducers of the most provocative type. An accidental encounter between a temporarily unstable homosexual and a youthful seducer might result in behaviour which would scarcely merit the condemnation and punishment appropriate to an unprovoked aggressive sexual assault. When doctors write as medical men their observations are generally of scientific character. The doctor writing as an individual cannot be expected to maintain the same degree of objectivity as his professional other self. . . . Let all doctors bear in mind that their opinions can be distorted and misinterpreted outside the medical orbit . . . and be correspondingly wary.

Obituary

CHARLES GIBSON LOWRY, M.D.
F.R.C.S.I., F.R.C.O.G.

The death occurred at his home in Donaghadee, County Down, on September 9, of Professor C. G. Lowry, a Pro-Chancellor and the emeritus professor of midwifery in the Queen's University of Belfast.

Charles Gibson Lowry was born in 1880, the eldest son of Mr. Samuel Lowry, of White Hill, Limavady, and educated at Foyle College, Londonderry, and Queen's College, Belfast. He obtained the degrees of M.B., B.Ch., B.A.O. of the Royal University of Ireland in 1903 and the M.D. degree with gold medal in 1906. In 1918 he became a Fellow of the Royal College of Surgeons in Ireland. At the Royal Victoria Hospital he was awarded the Coulter Exhibition, and was house-surgeon and house-physician there and in the Belfast Maternity Hospital. In 1907 he embarked on general medical practice, and a year later he, like so many Belfast surgeons who achieved success, obtained his first opportunity by being appointed to the honorary staff of the Ulster Hospital for Children and Women. There, as assistant gynaecologist, he quickly built up not only his reputation but a wide and lucrative practice as a gynaecologist and obstetrician.

In 1920, on the death of Professor Sir John Byers, he was appointed professor of midwifery in the Queen's University with his lifelong friend Mr, R. J. Johnstone as his colleague in the chair of gynaecology. This was the perfect partnership. In those days the Belfast Maternity Hospital was a small one and long since inadequate to the needs of the community. Although it had been for many years a recognized teaching hospital it is on record that Lowry said he had never heard a clinical lecture on midwifery until he gave one himself. On being appointed professor of midwifery he was invited to join the staff of the Maternity Hospital, and was elected an assistant gynaecologist to the Royal Victoria Hospital, with the most happy and far-reaching results. With the able co-operation of Dr. J. A. Lindsay, then professor of medicine, and of Professor R. J. Johnstone, clinical teaching was firmly established, and by their efforts the Royal Maternity Hospital was opened in 1933. It is to C. G. Lowry more than to any other that the Belfast school of obstetrics owes its present status.

His work was not confined to his own province of Ulster. He served for eight years on the General Medical Council as the Crown nominee for Northern Ireland. He was one of those who actively collaborated with Professor Blair Bell, of Liverpool, in the foundation of the Royal College of Obstetricians and Gynaecologists, and fittingly became a vice-president of the College. He was an external examiner in the University of Glasgow and an honorary president of the Glasgow Obstetrical and Gynaecological Society.

His own university honoured him by appointing him a Pro-Chancellor and a doctor of science, *honoris causa*. On his resignation from his chair in 1945 his friends and colleagues presented him with his portrait, painted by Mr. James Gunn. Lowry was also an honorary fellow and an ex-president of the Ulster Medical Society, and he was president of the Section of Midwifery and Gynaecology at the Annual Meeting of the B.M.A. in 1937. During the 1914–18 war he was invited to serve in the U.V.F. Military Hospital as an honorary captain, R.A.M.C., and with characteristic versatility achieved success as an orthopaedic surgeon.

C. G. Lowry was endowed with a multiplicity of gifts. He was the born surgeon, with capable and dextrous hands, but no man took greater care to develop his talents. Capable and resourceful in any emergency, he made it his business to see that emergencies were prepared for. In the best sense his was the genius which is the infinite capacity for taking pains. Nothing was left to chance. The most minor operation or normal accouchement was treated with the same meticulous care as the gravest surgical problem. His patients quickly discerned his qualities and placed their trust in his skill and his wisdom. Those who worked for him soon learned that they also worked with him, and realized that it was only fair that he should demand from them the same high standards which he so relentlessly set for himself; soon they rejoiced to share with him the effort and achievement. He was, in the modern phrase, "a good picker of chaps" and gathered about him a team of competent and enthusiastic disciples. It is not surprising that his advice was sought by many who valued his wise counsel given so freely and without stint of time or full consideration, and that at hospital staff meetings he was indeed an elder statesman. He had an amazing memory and "the experiencing mind." It seemed as if he never forgot a name or a face or a case-history. Of Presbyterian heritage, his quotations from scripture were accurate and timely adornments to the forceful and unforgettable teaching of the subjects which he knew and loved. He sought perfection not only in surgical technique but in everything which is part of the art of living.

After his retirement he delighted in his garden at Donaghadee, making "the crooked straight and the rough places plain," and exhibiting his expertise in remembering the botanical names of flowers and fruit trees.

He married Grace, the youngest daughter of Mr. M. Crymble, of Belfast. She survives him with their daughter Margaret, who is the wife of Professor C. H. G. Macafee, his successor in his chair. Of his four brothers one was Dr. James A. Lowry, of Fareham, and another is Mr. H. C. Lowry, of Belfast.

At the simple and beautiful service before his body was laid to rest, the Reverend Dr. D. Frazer-Hurst, in paying tribute to him, said:

"Few men have served their day and generation more faithfully. Few men have employed their gifts and abilities more unselfishly for the general good. Awards and distinctions came to him in recognition of his outstanding services, but he never worked for such rewards. His ambition was not to be famous, but to be serviceable; not to gain renown, but to honour his profession and extend the bounds of knowledge in his own sphere of work. A notable and very attractive feature of his character was the great respect and affection he bore to his parents. To fulfil the Fifth Commandment was no task for him, for he delighted to talk of his father and mother. Such was the man we knew, one who honoured his calling, both in his work and his character, a good man, full of faith and human kindness. 'Take him for all in all, we shall not look upon his like again.' He was loved and honoured in his life, and his memory will always abide, bright and unclouded in our hearts."—R. M.

N. G. W. DAVIDSON, F.R.C.S.Ed.

Mr. N. G. W. Davidson, honorary consulting surgeon to the Victoria Infirmary, Glasgow, died in Glasgow on August 30, aged 68.

Norman Grenville Walshe Davidson was born in Co. Antrim, Northern Ireland. He studied medicine in Edinburgh and obtained the triple qualification in 1908. For some years after that he practised in Spain, but he returned to this country in 1914 to join the R.A.M.C. He developed an interest in surgery and was later in charge of a surgical division in the Egyptian Expeditionary Force. In 1915 he had been admitted a Fellow of the Royal College of Surgeons of Edinburgh. For his war service he was appointed O.B.E. On demobilization he went to Glasgow and was appointed to the surgical staff of the Victoria Infirmary, and served that institution faithfully and well until he retired in 1946. Besides being a lecturer in clinical surgery to the University of Glasgow he was consulting surgeon to Kilmarnock Infirmary, and consultant in orthopaedics, a branch of surgery in which he was keenly interested, to Ayr County authority.

W. A. S. writes: Davidson was a real colleague, always ready to give of his best, and with whom it was a pleasure to collaborate. He worked hard—indeed, some of us thought too hard—but if there was work to do he was never satisfied until it had been completed. No case was too trivial for his careful attention, and he gave to his patients that confidence which made them feel that they, and they alone, were his chief concern. He was critical at times, but the criticism was always followed by his reason for finding fault and an explanation of how the mistake could be rectified and avoided in future. Probably he was his own sternest critic, and his work was as close to perfection as he could make it. He did not contribute greatly to the journals, but excelled as a clinician. With his students in the wards he was at his best and took infinite trouble to bring home to them what he considered the roots of the matter. Compensation cases were another of his interests, and in court his ready wit and that ability to anticipate the next move of the cross-examination stood him in good stead as an expert witness. A devoted husband and father, it was a great blow to him when his son Ian died in 1946 and a daughter in early childhood. He was a keen fisherman and motorist; but the loss of his sight ended these pleasures, and latterly he was unable to read. All through his illness his wife was his mainstay and sheet anchor; to her, their daughter, and two sons his colleagues, friends, and patients extend their sincere sympathy.

GEOFFREY EVANS, M.D., F.R.C.P.

Dr. George Graham writes: I do not think it is generally known that Dr. Geoffrey Evans played an important part in the preparation of the chart in which the temperature, pulse, and respiration rates are all graphed. Shortly after he qualified he spent some six months in the University Clinic at Basle. There he was struck with the way in which not only the figures for the temperature were graphed but also those for the pulse and respiration rate, though the type of chart was not at all easy to read. In 1912 he returned to St. Bartholomew's to serve as a house-physician to Dr. A. E. (later Sir Archibald) Garrod. There, with the assistance of Miss Norah Powell, then the sister of Mark Ward, and encouraged by Dr. Garrod, he redrew the hospital charts so that all three were displayed on one chart, though each had its separate section. This chart gives a much clearer picture of the state of the patient than the old-fashioned chart on which the temperature alone was graphed while the pulse and respiration rates were written in small figures. The medical council of the hospital adopted this form of chart in 1912, though it was some 15 years before it was used in every department. Some clinicians object to the new chart, as the fluctuations of the temperature are not as wide as in the old chart, and the unobservant may not appreciate the rise of a temperature to 99.4° F., but the graphing of the pulse and respiration rates makes it much easier for these variations to be appreciated. The use of this type of chart also renders the work of the nurses easier, as it is simpler to make a dot on the chart than to write a figure, and all nurses do not make their figures very clear. It must be a rare occurrence for a house-physician to be responsible for such an important innovation.

A correspondent writes: About a few persons legends grow after their death: about a very few legends grow up in their lifetime. Geoffrey Evans was of the latter. Of his dinner parties before the second world war, of his distinctive dress, of his incisive manner, of his humanity, and of his humanness much has been talked in the last week. His last publication was a compendium of medical knowledge. It is our infinite loss that he has taken his wisdom with him into the shadows. It is our joy that he knew those shadows to be the light. And rarely, too rarely, in our better moments we hear echoes of his teaching in our own voices used to our own patients.

Medico-Legal

MENTAL DEFECTIVES' ATTACK

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

Two former patients of Darenth Park Mental Hospital attacked and injured the hospital attendant and nurse who were taking them back by car to the hospital after they had absconded. They appeared recently before Mr. Justice Byrne at Maidstone Assizes.[1]

Both pleaded guilty, and there was accordingly no issue at the trial whether or not they were either of them insane within the M'Naghten Rules.

James Edward Kinsey was charged with wounding the attendant, whom he had stabbed five times in the neck with a pocket-knife, with intent to do him grievous bodily harm. Dr. William Grey, the Canterbury Prison medical officer, said that, although Kinsey, who had been working as a labourer on a daily licence, was a high-grade mental defective, he was not certifiable under the Lunacy Act. In sentencing him to seven years' imprisonment, Mr. Justice Byrne observed that he was fortunate not to be standing in the dock on a charge of murder, and that the sentence was very much shorter than it would have been but for his state of mind.

Josephine O'Shea, aged 18, who had been working on daily licence as a domestic servant when she absconded, was charged with assaulting the nurse and causing her bodily harm. Dr. Winifred Jagger, medical officer of Holloway Prison, described her as having the mental age of a child of 9. Mr. Justice Byrne ordered her to be detained as a mental defective under section 8 of the Mental Deficiency Act, 1913.

[1] *The Times*, June 26.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending September 1 (No. 35).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending September 1					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	35	4	9	—	1	51	6	18	—	3	790	262	51
Deaths	—	—	—	—	—	2	—	—	—	—			
Dysentery	152	32	72	3	1	156	9	107	—		419	112	64
Deaths		—		—			—		—				
Encephalitis, acute	10	—	—	—		5	—	1	—		5	2	—
Deaths		—			1		—			—			
Erysipelas			10	—	3			21	4	5			
Food-poisoning	123	12		3		160	14		2				
Infective enteritis or diarrhoea under 2 years				11	39				15	24			
Deaths	8		3	1	—	9		2	1	2			
Measles*	1,876	68	67	77	40	3,413	199	60	29	50	3,413	1,565	675
Deaths		—	—	—	—		1	—	—	—			
Meningococcal infection	36	4	12	1	2	33	1	14	1	2	70	33	25
Deaths		—	1				—	—					
Ophthalmia neonatorum	31	4	11	—		36	4	9	—		98	59	36
Pneumonia, influenzal	217	8	3	1		235	16	2	3		378	265	216
Deaths (from influenza)†	3	1	—	—	—	4	2	—	—	1			
Pneumonia, primary			134					94					
Deaths	133	14		11	5	96	13		4	3			
Poliomyelitis, acute:													
Paralytic	35	3	7	1		491	30	80	18	6	657	32	17
Non-paralytic	54	3											
Deaths§	1	—			—	14	—			—			
Puerperal fever			3				—	9					
Puerperal pyrexia‖	234	31	8	2		68	5	7	1		198	131	68
Scarlet fever	461	29	108	16	19	715	42	108	31	39	2,212	744	436
Deaths		—	—	—	—		—	—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			143	32				112	36				
(2) Tuberculosis, non-respiratory			30	14				23	4				
(1) Deaths	130	8	22	1	8	119	14	22	5	9			
(2) Deaths		3	5	—	2		3	3	1	4			
Typhoid fever	2	2	1	—	—	7	3	3	2	5			
Deaths¶	—	—	—	—		—	—	—	—				
Paratyphoid fever	37	1	—	4	2 (B)	6	1	2 (B)	—	1 (B)	71	23	12
Whooping-cough	2,727	107	297	62	78	3,671	325	223	42	100	3,671	1,618	1,198
Deaths	2	—	—	—	—	3	1	—	—	1			
Deaths (0–1 year)	181	25	30	7	14	175	21	31	8	14	341	295	175
Deaths (excluding stillbirths)	3,975	621	557	100	148	3,847	598	500	78	150	3,871	3,712	3,465
Annual death rate (per 1,000 persons living)			11·4					10·0					
Live births	6,646	1,169	756	218	395	6,880	1,054	783	185	385	8,699	6,879	5,960
Annual rate per 1,000 persons living			15·5					15·7					
Stillbirths	183	22	21			187	21	25			277	210	185
Rate per 1,000 total births (including stillborn)			27					31					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

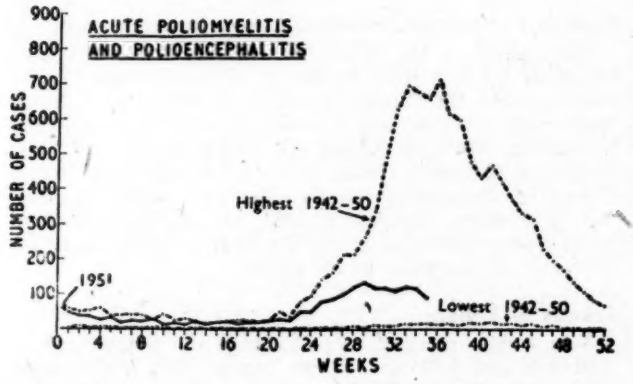
Vital Statistics

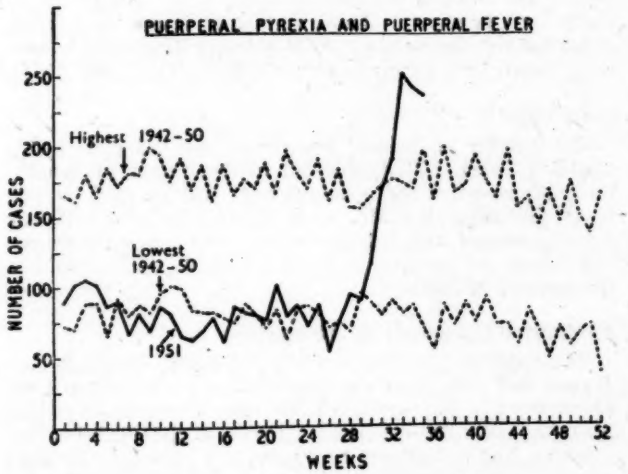
Poliomyelitis

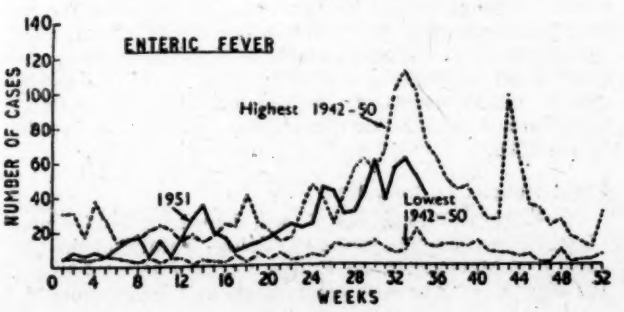
Poliomyelitis notifications in the week ending September 8 (with figures for the previous week in parentheses) were as follows: paralytic, 47 (35); non-paralytic, 39 (54); total, 86 (89). The outstanding feature of the week under review is the higher proportion of paralytic cases (55%). This is the highest ratio for any week in recent months, and shows a trend towards the experience of the other post-war years, when paralytic notifications were, on average, about twice as frequent as non-paralytic.

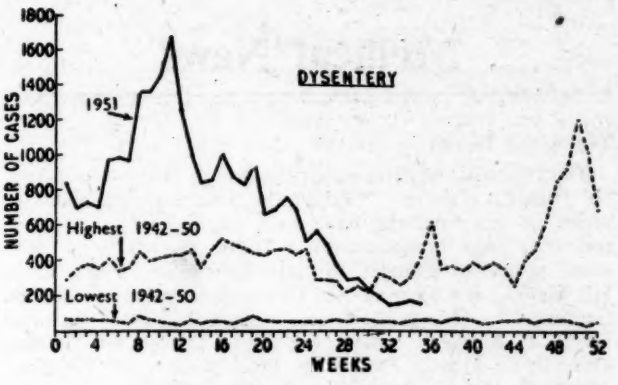
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus - - - - - - -, the figures for 1951 thus ———. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The incidence of infectious diseases continued to decline in England and Wales during the week ending September 1. The falls in the number of notifications included measles 476 and whooping-cough 221.

The incidence of measles declined throughout the country with only small exceptions. The largest falls were Lancashire 81, Durham 68, and Kent 66. The fall in the incidence of whooping-cough was most pronounced in the southern section of the country; in London and the south-eastern counties the notifications were 141 fewer than in the preceding week. The largest fluctuations in the local trends of whooping-cough during the week were an increase of 41 in Staffordshire and a decrease of 31 in Yorkshire West Riding. No change occurred in the local returns of scarlet fever, and the total notifications were 2 fewer than in the preceding week. (In last week's Table (p. 684) the number of notifications of scarlet fever in England and Wales should have been 463, not 436.) Twelve more cases of diphtheria were notified than in the previous week. The largest increase was of 7 in Warwickshire; all 8 cases in this country were notified in Birmingham C.B.

The notifications of paratyphoid fever were 9 fewer and those of typhoid fever 4 fewer than in the preceding week.

The number of notifications of acute poliomyelitis was the lowest for nine weeks. A decrease of 25 was recorded in the number of paralytic and 2 in the number of non-paralytic cases. The chief centres of infection were Lancashire 11, Yorkshire West Riding 9, London 6, and Warwickshire 6.

A fall of 22 was recorded in the number of notifications of dysentery. The largest returns during the week were London 32 (Lewisham 11), Lancashire 19, Yorkshire West Riding 10, and Kent 10.

Week Ending September 8

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 499, whooping-cough 2,576, diphtheria 40, measles 1,387, acute pneumonia 196, acute poliomyelitis 86, dysentery 131, paratyphoid fever 32, and typhoid fever 4.

Should a doctor tell his patient that he has cancer? Two American doctors offer some advice on this problem (*J. Amer. med. Ass.*, August 15, p. 1547). First the physician should, obviously, be absolutely certain of his diagnosis, and, if he does tell the patient, should stress the necessity of treatment, pointing out that no disease is absolutely fatal. On the whole it is best to wait until the patient asks, as it is inevitable that if he really wants to know he will finally ask. The way in which the question is put will offer a guide to the answer to be given. "I don't have cancer, do I?" implies that a negative reassurance is being sought, whereas a patient interested in hard facts is generally a realist who can be told the truth. Other considerations include whether or not the family should be told, and the doctor must decide whether or not their knowing would help his patient. When the patient himself knows he has cancer he is the person, with the help of his doctor, to decide who should be told.

Medical News

The King's Health

The following bulletin about the King's health was issued on Tuesday evening: "During the King's recent illness a series of examinations have been carried out, including radiology and bronchoscopy. These investigations now show structural changes to have developed in the lung. His Majesty has been advised to stay in London for further treatment." The bulletin was signed by nine doctors: Dr. G. R. Mather Cordiner, Sir Daniel Davies, Sir Thomas Dunhill, Sir Horace Evans, Dr. Peter Kerley, Dr. Geoffrey Marshall, Mr. C. Price Thomas, Sir John Weir, and Sir Robert Young.

Family Doctor

The October issue of *Family Doctor* will be published on September 27. In this issue Professor Dugald Baird discusses "The Emotions in Pregnancy," and Dr. C. M. Billington writes on "Children at Boarding Schools." Edible fungi are described in John Ramsbottom's "Toadstools for Lunch." The work of the Metropolitan Water Board is outlined in "From Thames to Tap." Other topics covered in this issue include: "School for Diabetic Children," "How High is a Housewife," "Fresh Fruit from your Garden," "Whooping-cough Vaccine," "Knee Injuries," and "Double Joints." Copies can be obtained from any newsagent or direct from the Publishing Manager at B.M.A. House.

Training for Medical Librarians

On September 27 at 6.45 p.m. the first full-scale course of lectures on medical librarianship to be given in this country will start at the North-western Polytechnic, Prince of Wales Road, London, N.W.5. The lectures will be given weekly and will deal with such subjects as the history and present state of medical libraries, classification and cataloguing, periodicals and abstracting journals, literature of medical history, medical biography and individual bibliography, special forms of medical literature, principles of reference work, current guides to medical literature, Government publications, medical nomenclature, and special categories of medical libraries.

Overture to Moscow

The Medical Association for the Prevention of War has sent a letter to Moscow outlining the objects of the association and offering to establish friendly contact with Soviet medical men. A similar letter to medical organizations in America is also to be sent. Two working parties have been set up, to consider the psychopathology of war and the ethical responsibilities of doctors in relation to war. The committee is looking into the possibility of making an active contribution to medical relief work in Korea.

Emergency Bed Service: Applications and Admissions

During the seven days ending September 17 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 676, of which 92.15% were admitted. This information will in future be published weekly in these columns. The applications include those from general practitioners and those from hospitals wanting to transfer patients from their casualty or outpatient departments. The gap between the number of applications and the number admitted is not composed entirely of cases that fail to be admitted. Some are cases withdrawn by the doctor or hospital while the E.B.S. is still working on the case, and some cases are of patients who refuse to go to hospital when a bed has been found or who die before admission.

COMING EVENTS

Welsh National School of Medicine

The opening sessional address of the Welsh National School of Medicine will be given on Thursday, October 4, by Dr. H. P. Himsworth, secretary of the Medical Research Council.

Lectures on Ophthalmology

A series of four lectures on ophthalmology will be given in the Department of Ophthalmology of the University of Glasgow on Wednesdays, October 3, 10, 17, and 24, at 8 p.m. Details will be published in the "Societies and Lectures" column of the *Journal*.

Royal Army Medical College

The Royal Army Medical College has arranged a series of evening lectures to be delivered in the Lecture Theatre of the college (entrance in John Islip Street, London, S.W.) on October 10 and 25, November 15, December 6, 1951, January 10 and 31, February 21, March 13, April 3 and 24, and May 13, 1952, at 5 p.m. The programme will cover professional subjects of interest to both Service and civilian doctors, and will be open to all medical practitioners without fee. Details will be published in the *Journal* week by week under "Societies and Lectures."

Comfort Crookshank Award for Cancer Research

The council of the Middlesex Hospital Medical School has made the first triennial award of the Comfort Crookshank Award for Cancer Research to Professor John J. Bittner, professor of cancer research in the University of Minnesota. Professor Bittner will deliver a lecture on "The Genesis of Mammary Cancer in Mice" in the clinical lecture theatre of the medical school (Mortimer Street, London, W.) on Monday, October 8, 1951, at 4.30 p.m. Medical practitioners wishing to attend the lecture should apply for tickets to the secretary of the school.

Friends of Vellore

Two public meetings will be held on October 10 at 3.30 p.m. and 6.30 p.m. at the Caxton Hall, Westminster. During the evening the new coloured film "Adventure of Faith" will be shown. Those wishing to attend the meeting should inform the secretary, Miss Margery Chapman, Annandale, North End Road, London, N.W.11 (Tel.: SPE 2311).

Osler Club

The meeting on Friday, December 7 at 7.45 p.m., at 11, Chandos Street, will be devoted to the history of medical illustrations, when the opening paper will be read by Mr. E. P. Goldschmidt. Mr. R. B. Fishenden, editor of *The Penrose Annual*, and technical editor of *King Penguin Books*, will speak on modern methods of book illustration. A discussion will follow.

Paediatrics Congresses at Montevideo

The 3rd Pan-American and the 3rd South American congresses will take place simultaneously at Montevideo from December 2 to 8 at the Clinics Hospital. They will be divided into four sections—medicine, surgery, social medicine and teaching, and miscellaneous. Papers (not exceeding 10 pages double spacing) should be submitted to the secretary not later than September 30, written in one of the official languages (Spanish, Portuguese, French, or English), together with a 300-word summary. Registration fee is 25 Uruguayan dollars, and all details may be obtained from the secretary, Congresos de Pediatria de Montevideo, 1246, Av. 18 de Julio, Montevideo.

Lloyd Roberts Lecture, 1951

Dr. F. M. R. Walshe, F.R.S., will deliver the 22nd Annual Lloyd Roberts Lecture in the Physiology Theatre of the University of Manchester, on Friday, October 26, at 4.30 p.m. His subject is "The Arts of Medicine and their Future."

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Sunday

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Adolph Tuck Hall, Woburn House, Upper Woburn Place, London, W.C., September 23, 3 p.m., "*The Frontiers of Psychiatry*," Presidential Address by Dr. Emanuel Miller.

Tuesday

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—September 25, 5 p.m., "*The Use of Bone in Reconstructive Surgery*," by Mr. Rainsford Mowlem; 6.15 p.m., "*The Surgery of the Bile Ducts*," by Mr. Rodney Maingot.

Wednesday

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—September 26, 5 p.m., "*Non-malignant Surgical Affections of the Cardiac End of the Stomach*," by Mr. Norman Tanner; 6.15 p.m., "*Ureter in Gynaecology*," by Mr. Charles Read.

Thursday

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—September 27, 5 p.m., "*The Painful Shoulder*," by Mr. Ronald Furlong; 6.15 p.m., "*Pott's Fracture*," by Professor George Perkins.

Friday

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, Cavendish Square, London, W.—September 28. 7.30 p.m., "*The Pathogenesis of the Jarisch-Herxheimer Reactions*," by Dr. Albert Heyman. Discussion.

MIDDLESEX COUNTY MEDICAL SOCIETY.—At Chase Farm Hospital, Enfield, Middlesex, September 28, 4.30 p.m., annual general meeting. "*Emergency Surgery*," Chairman's address by Mr. H. O. Blauvelt.

●ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS, 58, Queen Anne Street, London, W.—September 28, 2.30 p.m., "*The Princess Charlotte of Wales: A Triple Obstetric Tragedy*," William Meredith Fletcher Shaw Memorial Lecture by Sir Eardley Holland.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—September 28, 5 p.m., "*The Principles of Treatment in Burns*," by Mr. William Gissane; 6.15 p.m., "*Obstructive Hydrocephalus*," by Mr. J. Pennybacker.

APPOINTMENTS

Dr. John Marshall, *M.C.*, T.D., has been appointed Honorary Surgeon Oculist to the King in Scotland, in succession to Mr. A. H. H. Sinclair, who has resigned.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—*Senior Registrar in Chest Medicine at Cambridgeshire Chest Clinic*, Ann H. Willcocks, M.B., B.S., M.R.C.P. *Ophthalmic Registrar at East Suffolk and Ipswich Hospital*, John Monckton, Esq., M.R.C.S., L.R.C.P., D.O.

LASSMAN, L. P., M.B., B.S., F.R.C.S., Assistant Regional Neuro-surgeon, Newcastle-upon-Tyne Regional Hospital Board.

MACKENZIE-WINTLE, HECTOR A., M.R.C.S., L.R.C.P., D.P.H., Medical Officer of Health to South Oxfordshire Combined Districts (Henley Borough and Rural District, Thame and Bicester Urban Districts, Bullingdon and Ploughley Rural Districts).

MANCHESTER REGIONAL HOSPITAL BOARD.—*Consultant Orthopaedic Surgeon, Wigan and Leigh Hospitals*, F. R. Zadik, M.B., Ch.B., F.R.C.S. *Consultant Orthopaedic Surgeon, Withington Hospital, Manchester, and Stockport and Macclesfield Hospital Areas*, J. C. F. Cregan, M.B., B.S., F.R.C.S. *Assistant Anaesthetist, Lancaster and Kendal Hospitals*, A. K. Karfoot, M.B., Ch.B., D.A.

MAWSON, S. R., M.B., B.Chir., F.R.C.S., D.L.O., Assistant Ear, Nose and Throat Surgeon, King's College Hospital Group, London.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Gavey.—On September 3, 1951, at Westminster Hospital, London, S.W., to Marjorie (formerly Guille), wife of C. J. Gavey, M.D., F.R.C.P., a daughter.

Goodsir-Cullen.—On August 10, 1951, at Ipswich Maternity Home, to Dr. and Mrs. Ernest Goodsir-Cullen, a son—Niall Jonathan.

Scrivener.—On September 13, 1951, at Aldwick, Sussex, to Patricia, wife of Major J. P. Scrivener, M.B.E., R.A.M.C., a son—John Rupert.

Simons.—On September 11, 1951, at Manygates Maternity Hospital, Wakefield, Yorks, to Joan (formerly Garside), M.B., Ch.B., wife of E. L. Simons, M.B., B.Chir., a daughter.

DEATHS

Hunter.—On September 16, 1951, at his home, Epsom, Surrey, John Bowman Hunter, C.B.E., M.C., M.Ch., F.R.C.S., aged 61.

Jack.—On September 10, 1951, at Holmwood, Kilwinning, Ayrshire, James Jack, M.D.

McGrath.—On September 15, 1951, Annie Margaret McGrath, M.B., B.S., D.P.M., of St. Christopher's, Wilkin's Green Lane, Hatfield, Herts.

Mathieson.—On September 10, 1951, at his home, 14, Heyrham Hall Grove, Heysham, Lancs, James Moir Mathieson, M.B., Ch.B., late of Sheffield.

Wright.—On September 11, 1951, at The Brae, Lower Bourne, Farnham, Surrey, Maurice Beresford Wright, O.B.E., M.D.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Counteracting Action of A.C.T.H.

Q.—*Is there any antidote to A.C.T.H.?*

A.—An antidote is usually taken to mean a substance which opposes or annuls the action of a poisonous or toxic substance. A.C.T.H. is a physiological hormone, so strictly speaking there is no antidote. The duration of its effect in the body is very brief, and the effect of a single dose probably lasts not longer than four hours, so that treatment is easily withdrawn. The effects of continued dosage are of course cumulative. Untoward responses of moderately acute onset include oedema and potassium deficiency. Usually withdrawal of the hormone is sufficient to combat these troubles, but a mercurial diuretic and possibly digitalis therapy may be needed. The use of the mercurial may aggravate the tendency to potassium deficiency and therefore be dangerous, unless the possible requirement for more potassium is borne in mind. Increased dosage of insulin may be required in diabetics given the hormone. The response to insulin is poor while A.C.T.H. is administered. From the physiological standpoint there is evidence to suggest that the growth hormone has some action opposing that of A.C.T.H.—certainly they have opposite effects on growth. Growth hormone favours nitrogen anabolism, A.C.T.H. nitrogen catabolism. But both hormones favour the development of diabetes under certain conditions.

Multilingual Upbringing

Q.—*In this district Welsh is the medium of instruction in all schools for young children. No English is used until the child is 7, when it is introduced as a secondary language, though many children come from English homes. Are psychological disturbances more common in children whose basic language is changed on going to school, and do they tend to be backward compared with other children?*

A.—To have to cope with two different languages is undoubtedly somewhat of a strain, and one might expect emotional disturbances to rise slightly in frequency among children bilingually educated. Though the situation cannot have been uncommon among the children of immigrants in the United States, and in the countries of Eastern Europe, there appears to be no observational study on the point. Smith, M. E. (*J. Genet. Psychol.*, 1949, **74**, 305), has reported on Chinese children educated in Honolulu. English was the preferred language. The average total vocabulary of these children was nearly equal to that of monoglot controls; but if words whose meaning was known in both Chinese and English were counted once only, the standard reached was only 80% of that of controls, and in English and Chinese separately 60% and 40%. The author believed that the bilingual child was to some extent handicapped.

Fluoride Poisoning

Q.—*What are the dangers of exposure to the fumes of ammonium bifluoride? A girl of 18 who works with this substance has recently had septic fingers, tonsillitis, and pain over the left lower ribs, with breathlessness on exertion lasting for a month. Are these conditions likely to be related to her employment?*

A.—Ammonium bifluoride is an acid salt, $NH_4F.HF$, used for glass etching, as a flux in magnesium foundries, and as a disinfecting agent in breweries. The risks in its use are those of hydrofluoric acid and fluorides in general. The hydrofluoric acid (HF), which is a component of this

double salt, can produce severe injury to the skin, leading to ulcers that are slow to heal. Fluorides are irritating to mucous membranes, and severe nasal irritation has been reported in magnesium founders exposed to fluoride fumes. The septic fingers and tonsillitis of this girl may therefore be attributable to exposure to ammonium bifluoride.

The symptoms of pain over the left lower ribs with breathlessness on exertion, however, are not characteristic of acute fluoride intoxication. The symptoms of acute poisoning are vomiting, abdominal pain, diarrhoea, convulsions, generalized muscular weakness, and collapse. Chronic fluorosis usually takes some years to develop, and the bony and dental changes are usually well marked.

Spina Bifida and Asthma

Q.—*A midwife of wide experience once told me that in every case of spina bifida which she had encountered there was a history of asthma in a near relative. Curiously, as it seems, this has been true of each case of spina bifida which I have seen since. Is there any known association?*

A.—This is a useful suggestion to place on record. It may indeed be that here is a rather unlikely connexion that has been overlooked. On the other hand one feels that it is improbable that those who have made extensive studies on spina bifida would have missed such an association; so far it does not seem to have been recorded.

Nodules in the Back

Q.—*What are the latest views on the pathology and treatment of the tender fibrotic nodules sometimes found in the lumbar-sacral region?*

A.—The lumbar-sacral region normally contains fatty lobules, well defined, of variable size, and not infrequently relatively mobile. Some of these have been shown to be herniations from beneath the deep fascia (Copeman, W. S. C., and Ackerman, W. L., *Quart. J. Med.*, 1944, 13, 37). They consist of normal fatty tissue. In a few individuals one or other of these nodules becomes tender, possibly as a result of trauma. This may subside spontaneously, or if the patient becomes aware of the lump the complaint may persist. The treatment recommended is vigorous needling and injection with procaine solution.

Genetics of Microphthalmia

Q.—*A woman of 30 with a normal female child aged 3½ years gave birth last year to a female child with microphthalmia and bilateral cataract. The appearance was mongoloid, the fingers were slightly webbed, and there was a marked space between the great toe and the next on each foot. This child survived for six months, when she developed pneumonia and died. The parents are first cousins, but there is no history of mental disease in the family. What are the chances of a further child being abnormal?*

A.—A recent comprehensive study by Sjögren and Larsson (*Acta psychiat., Kbh.*, 1949, Suppl. 56) is of much help in attempting to answer this difficult question. In microphthalmia the important genetic distinction lies between those with and those without coincidental mental deficiency. It is probable that this child belongs to the former group. Apart from the mongoloid appearance mentioned in the question skeletal defects are extremely common in microphthalmia associated with mental deficiency but very rare in other cases of the condition. Some families show sex-linkage, but that is ruled out here as the child was a girl. If, however, there is one uniform mode of inheritance of microphthalmia with mental deficiency, this could only be a recessive partially sex-linked gene, and the chance that a subsequent child would be affected is about one in ten. It is more likely, however, that there are different modes of inheritance and that the causation is exogenous in a fairly high proportion of cases. Sjögren and Larsson are inclined to dismiss the hypothesis that some instances may be due to an ordinary recessive gene (they found 6% first-cousin marriages amongst the parents as against 2–3% in the Swedish rural population), but some may doubt this conclusion. If only one could dismiss this possibility with confidence, the chances would be excellent—perhaps one in twenty or even considerably less. But is the cousin marriage a coincidence? May not a recessive gene be involved sometimes? If so, the chance is one in four. Perhaps the parents could be told that it is likely that the chance is small, but that there is a not very great possibility that it might be as high as one in four.

Later Treatment of Addison's Disease

Q.—*A man of 43 diagnosed as having Addison's disease and discharged from hospital with a deoxycortone implant still has considerable weakness of the legs, tachycardia on exertion, complete absence of adrenaline response to excitement or emotion, and is impotent. What is his prognosis?*

A.—Although theoretically deoxycortone is incomplete replacement therapy in Addison's disease, most patients respond quite well with the correct dose. Excessive dosage may produce weakness or paralysis of the limbs resulting from excessive excretion of potassium and low potassium in the tissues, and tachycardia may also occur. There may or may not be evidence of water retention—for example, crepitations at the base of the lungs. As to impotence, this may persist even with adequate deoxycortone therapy, and the supplementary use of testosterone or methyl testosterone is advocated. These substances have water-retaining action as well, and this must be considered, particularly if testosterone is implanted together with deoxycortone. The absence of adrenaline response is unusual, as is complete destruction of the medulla.

Treatment of Residual Oedema due to Erysipelas

Q.—*What treatment is advised for residual lymphatic swellings of the leg following attacks of erysipelas and lymphangitis several years ago? Elastic crêpe bandaging and gravitational drainage with massage have been tried without much success.*

A.—It is essential to prevent further attacks of erysipelas by attention to foot hygiene, especially by the treatment of epidermophytosis. If the oedema is mild, it can be adequately managed by the permanent use of thigh-length stockings of two-way-stretch latex yarn. If it is severe and disabling, then there is a good case for a thorough Sistrunk operation with the excision of redundant tissues and skin and the laying of the thin skin-flaps on the muscles after they have been stripped of their fascia. The leg must be oedema-free before operation. After the operation long elastic bandages should be constantly worn, and in very severe cases Unna's bandages may be needed.

Correction.—We regret that an error occurred in the paper entitled "Observations on all Births (23,970) in Birmingham, 1947" by Professor T. McKeown and Dr. J. R. Gibson in the *Journal* of September 1, p. 513. The fourth sentence in the penultimate paragraph should read: "This possibility is not yet in sight, but it can only be delayed by a practice which groups malformations with other causes of death."

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